INCIDENCE AND ENVIRONMENTAL RISK FACTORS FOR PSYCHOSIS IN FIRST GENERATION MIGRANTS IN NORTHERN ITALY

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INCIDENCE AND ENVIRONMENTAL RISK FACTORS FOR PSYCHOSIS IN FIRST GENERATION MIGRANTS IN NORTHERN ITALY

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Abstract

Whilst the excess of psychosis among migrants is a well defined phenomenon in Northern Europe, it had not been demonstrated in Southern Europe. Moreover : 1) most studies focused on ethnic minorities and not on first generation migrants; 2) there are not studies conducted in contemporary times involving internal migrants; 3)published studies have mostly focused on risk factors in the post migration phase (such as ethnic fragmentation, unemployment, etc).

My PhD project aimed to : 1) Verify whether there was an excess of psychosis among migrants in Italy 2) Understand the role of known environmental risk factors for psychosis (such as substance use, being single/living alone, being unemployed and low level of education) in the development and course of psychosis in migrants.

I used data collected in Bologna West as an incidence of first-episode psychosis (Bo-FEP) study. All first episode psychosis patients (FEP) age 18 to 65 yrs old, presenting to the Bologna Mental Health Centres between January 2002 and December 2010, resident within defined catchment areas in Bologna, and without any previous contact with health services for psychosis, were identified and invited to take part in this project. I also used follow-up data collected 1 year after the first contact of FEP patients with services.

My thesis contains 2 published papers and 1 accepted paper. (Tarricone et al., 2012; Tarricone et al., 2014; Tarricone et al, accepted with revisions), The overall Incidence Rare standardised for age and gender in the Bo-FEP study was 16.4 per 100,000 person-years (95% CI, 13.9-18.9). The Incidence Rate Ratio was 1.93 (1.19-3.13, p=0.007) for internal migrants and 1.79 (1.06-3.02, p=0.03) for external migrants compared to natives. Substance users had a significantly higher rate of hospitalizations during the 12 months follow-up after adjusting for age, gender and other potential confounders (OR 5.84, 95% CI 2.44-13.97, p≤0.001)

In addition I have reviewed the relevant literature, described the background and overall methodology of the study, discussed the limitations and written a conclusion.

Organization of the thesis

My PhD Project aims to identify any excess of psychosis in migrants in Northern Italy and to explore possible explanations for this phenomenon. This thesis comprises a total of 7 chapters. In chapter one I review the current literature with regard to risk factors for psychosis in migrants, focusing particularly on social risk factors. Then the aims and hypotheses are presented in Chapter two. In chapter three (methodology) I will describe the design of the first episode study that my PhD is based upon. In chapters four, five and six I present and discuss 3 accepted first author papers disseminating the results of the Bologna First Episode Psychosis Study (Bo FEP). These describe the incidence of psychosis in migrants, risk factors for psychosis in migrants, the outcome of psychosis in migrants and a unique study of internal migration (mostly from Southern Italy). Chapter seven draws the studies together to discuss the limitations of the work, how this work has advanced the field and future directions.

Table of Contents

Table of Tables

Table of Figures

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Glossary

- *Environmental risk factors*: environmental risk factors are defined as a set of factors and circumstances that interact with genetic predisposition to influence the risk of psychosis development trough life. Psychotic syndromes can be understood as disorders of adaptation to social context. Although heritability is often emphasized, onset is associated with environmental factors such as early life adversity, growing up in an urban environment, minority group position and cannabis use, suggesting that exposure may have an impact on the developing 'social' brain during sensitive periods (Dean & Murray, 2005; van Os et al., 2010).

- *Ethnic density*: proportion of ethnic minorities in a defined area (Boydell et al., 2001)

- *Migration*: Migration can be defined as the process of going from one country (external migration), region or place (internal migration) of residence to settle in another for the purposes of settling down either permanently or for a prolonged period. Such a shift can be for any number of reasons, commonly economic, political or educational. The process is inevitably stressful and stress can lead to mental illness. Migrants may move en masse or singly. For example, people who migrate for economic or educational reasons may move singly and at a latter date be joined by their families, whereas people who move due to political reasons may move en masse but with or without their families. urban-rural migration within the same country is not being discussed here (Bhugra & Becker, 2005).

- *Social capital*: social capital can be considered as a group of features related to the social organization of a neighbourhood that, collectively, "facilitate coordination and cooperation for mutual benefits" (Putman, 1993, p,36) (Kirkbride et al., 2007) . Kirkbride reported (2007) that the most commonly used definition of social capital in the health sciences originates from the political scientist Robert Putnam (1993, p. 36), who suggests that social capital consists of five principal characteristics :

    - 1) Community networks, voluntary, state, personal networks and density.

    - (2) Civic engagement, participation and use of civic networks.

- (3) Local civic identity : sense of belonging, solidarity and equality with local community members.
- (4) Reciprocity and norms of cooperation, a sense of obligation to help others and confidence in return of assistance.
- (5) Trust in the community.

- *Social defeat stress*: the chronic social defeat stress (CSDS) model is based in the induction of “social subordination” caused by short periods of struggle and continued fellowship with a dominant animal. A number of hierarchical relation studies show that animals that have been “subordinated” by the dominant individuals of the same species suffer signs of stress (Lagerspetz and Tirri 1961; Koolhaas et al. 1997) including social avoidance, anxiety, decreased grooming, hyperactivity, and increased vulnerability to addiction (Krishnan et al. 2007; Rossi et al. 2008; Denmark et al. 2010). Moreover, significant changes in brain function, physiology, and neurotransmitter and hormone levels have been reported (Bjorkqvist 2001; Rohde 2001; Berton et al. 2006; Lutter et al. 2008; Wagner et al. 2011).

- *Urban/rural areas*: the definition of urban/rural areas is based on both qualitative and quantitative criteria that may include any combination of the following: size of population, population density, distance between built-up areas, predominant type of economic activity, conformity to legal or administrative status and urban characteristics such as specific services and facilities. Although statistics classified by urban/rural areas are widely available, no international standard definition appears to be possible at this time since the meaning differs from one country or area to another. The urban/rural classification of population used by UN is reported according to the national definition (Social and Demographic Statistics: Classifications of Size and Type of Locality and Urban/Rural Areas. E/CN.3/551, United Nations, New York, 1980; Demographic Yearbook 2012 UN)

List of Abbreviations

- A: Asians
- AC: African-Caribbeans
- Af: Africans
- Am: American
- B: Black
- BA: Black African
- BC: Black Caribbean
- BME: Black and Ethnic Minority
- BO: Black Other
- Br: British
- C : Chinese
- CMHC: Community Mental Health Centre
- Ctr: controls
- D: Dutch
- DUP : Duration of untreated psychosis
- E: European
- EE: East European
- EM: External Migrants
- F: Finns
- FEP: First Episode Psychosis
- I: Irish
- IM : Internal Migrants
- In: Indian
- Ir: Iraqis
- Is:Israeli

- G: Greek
- M: Moroccans
- ME: Middle East
- MHD . Mental Health Department
- NA: Natives
- Na: Netherlands Antilleans
- NBW: Non British White
- NW: Non White
- O: Other
- OW: Other White
- S: Surinamese
- SC & T: social cohesion and trust
- Sw: Swedish
- T: Turks
- U: Unknown
- W: Western
- WA: West Africa
- WB: White British
- WI: West Indian
- Y: Yugoslavia

Chapter 1: Literature Review and Background

1.1 Reviewing the evidence on high rates of psychosis in migrants

The first studies showing an increased incidence of schizophrenia and other psychotic disorders in migrants date back to the thirties, when Odegaard (1932) noted a markedly increased incidence of hospital admission rates for schizophrenia in Norwegian immigrants in the United States compared with Norwegians who did not migrate (1932). Odegaard (1932) hypothesized that the explanation for the excess of mental disorders found in his fellow immigrants was that the more vulnerable people migrated and this theory took the name of “selective migration." This theory has long been supported by observations such as the higher prevalence of psychiatric admissions among immigrants than natives (Schrier, van de Wetering et al. 2001).However, several observations have disconfirmed the hypothesis of selective migration, and called the attention of epidemiologists to environmental factors that can explain the so-called "excess of psychosis" in immigrants. As second generation migrants have grown up, there has been a further unexpected rise in the incidence of psychotic disorders among immigrants amongst the second generations (Cantor-Graae and Selte, 2005; , Bourque, van der Ven et al. 2011), thereby making it likely that social factors may be playing a part in the genesis of psychosis among migrants. Moreover, even Odegaard (1932) observed that rates were high among immigrants who had been in US for 10-12 years, suggesting that environmental factors in the countries where people migrated could play an important role. Finally, Selten et al. (Selten, Cantor-Graae et al.2002) tested Ødegaard's hypothesis: the authors imagined that migration from Surinam to the Netherlands subsumed the entire population of Surinam and not solely individuals at risk for schizophrenia. Even if everyone who would have developed psychosis in Surinam had migrated, the incidence of schizophrenia in Surinamese in the Netherlands would still be higher than for the native Dutch population. Therefore they concluded that selective migration cannot solely explain the higher incidence of schizophrenia in Surinamese immigrants to the Netherlands.

However, as recalled by Bhugra (Bhugra, Hilwig et al. 1996) two other hypotheses must be disconfirmed before focusing on the hypothesis that high rates of psychosis in migrants are due to stress related to migration: 1) sending countries have high rate of

psychosis; 2) misdiagnosis of psychosis among migrants. About the first one, studies conducted in Jamaica (Hickling, Rodgers-Johnson 1995) Trinidad (Bhugra, Hilwig et al. 1996) and Barbados (Mahy, Mallett et al., 1999) have revealed incidence rates of psychosis lower than observed for migrants from these countries in the UK. In addition, there is no evidence that biological risk factors for schizophrenia(such as obstetric complications and viral infections) are more common or have a greater effect in the Black-Caribbean immigrant population (Fearon and Morgan 2006) Regarding the latter hypothesis, misdiagnosis, we must remember that some authors have suggested that there are possible misunderstandings between doctors and patients with religious beliefs and traditions different from Western ones and, as a consequence, emotional distress in these populations is misdiagnosed as schizophrenia (or psychosis more broadly) (Littlewood and Lipsedge 1981). In the meta-analysis of Selten &Cantor-Graae (2005), the relative risk of developing schizophrenia for the first-generation immigrants was 2.9 and increased to 4.5 for second generation immigrants. In a recent meta-analysis, Bourque et al (Bourque F, van der Ven et al. 2011) showed similar risk between the first (OR2.3) and second generation (OR2.1) migrants. Moreover, Bourque and colleagues (Bourque F, van der Ven et al. 2011) identified risk differences related to racial-ethnic group and the host community: in the UK black minorities showed higher risk, while in the Netherlands the more recent North African migrants where at higher risk. Thus, it's very intriguing to understand what are the characteristics of each specific host society that interact with each specific type of migrants and ethnic minorities (first-or next-generation; economic migrants or political migrants, etc.) to increase the risk of psychoses. It seems necessary to look for the risk of psychosis in the "immigrant status" rather than in the "migrants": “Immigrant status” signifies the special meeting between the migrant and the welcome- country and the nature of this meeting could explain the psychosis risk for migrants in different countries.

Recent points of view consider the excess of psychosis among migrants as a phenomenon linked to the complex interaction between biological vulnerabilities and environmental factors (cultural and socio-economic) during the entire migration process and settlement. Morgan et al (Morgan, Charalambides et al. 2012) proposed a sociodevelopmental model of psychosis to capture this. The environmental factors can act both individually and socially and can schematically be placed in the 3 phases of the

migration process (Bhugra and Becker 2005): during the pre-migration phase (obstetric complications, infectious factors, vitamin D deficiency), during the migratory phase (trauma of the journey, preparing to migrate, etc), and during the post migration (discrimination, unemployment, low socioeconomic status, racism, isolation, "urbanicity" and ethnic density).

Population based (first contact), incidence studies, possibly with a healthy control group, are able to provide evidence for the pathogenetic role of these factors in psychosis in migrants. These studies will now be reviewed.

1.2 **Method**

A literature review was conducted to identify population survey and service based studies into first episode psychosis (FEP). A study was considered eligible if:

- the study presented data on First episode psychosis (FEP) for both one (or more) ethnic minority group that had migrated to the country where the study was carried out and the ethnic majority in that same country;

-it was carried out in a general population or health services setting (community mental health and/or hospitals and/or primary care setting);

-the sample included adult patients;

-it was published in English as a full report.

Studies providing data on psychosis in specific groups not representative of the general population (e.g. patients with specific physical illnesses, such as diabetes or hypertension) were excluded.

Studies were identified by searching three electronic databases: MEDLINE, PsychINFO, and EMBASE using the following search strategies: “migration AND psychosis AND risk factors”. A second search was performed with the following terms: “(((predictors OR risk factors OR etiology)) AND (migrants OR non-natives OR immigrants OR migration)) AND (psychosis OR psychotic disorder OR schizophrenia illness OR schizophrenia disorder OR schizophrenia spectrum disorders)” The search was supplemented by references provided by personal bibliographies of the investigators and by hand searching content

pages of journals considered relevant to the topic (e.g., Transcultural Psychiatry and Ethnic & Health, International Journal of Social Psychiatry, Research on Social Work Practice, Psychiatric Research, etc). The search was run in June 2012 and updated in January 2013.

Three reviewers (see acknowledgements) independently checked the title and abstract of all identified records and subsequently read the full text of papers screened to assess their eligibility.

Using a predefined data extraction sheet, the following data were extracted for each study: year and country of publication; study design; setting; classification strategy for ethnic definition (census information, self-report or third-party report); sample source, size and characteristics (age, gender, language, ethnic group distribution and migrant status), screening and diagnostic tool used; incidence of psychosis and incidence differences (unadjusted or adjusted) with confidence intervals (CI) and P value; risk factors for psychosis.

1.3**Results**

Figure 1.1 shows a flow chart of the studies included and excluded. After reviewing the full text ,we found 55 studies (Table 1.1). Most of these studies come from England (22 studies) and 13 of these papers belong to the AESOP study (Aetiology and Ethnicity in Schizophrenia and Other psychoses).

Figure 1.1 Flow chart of the studies included

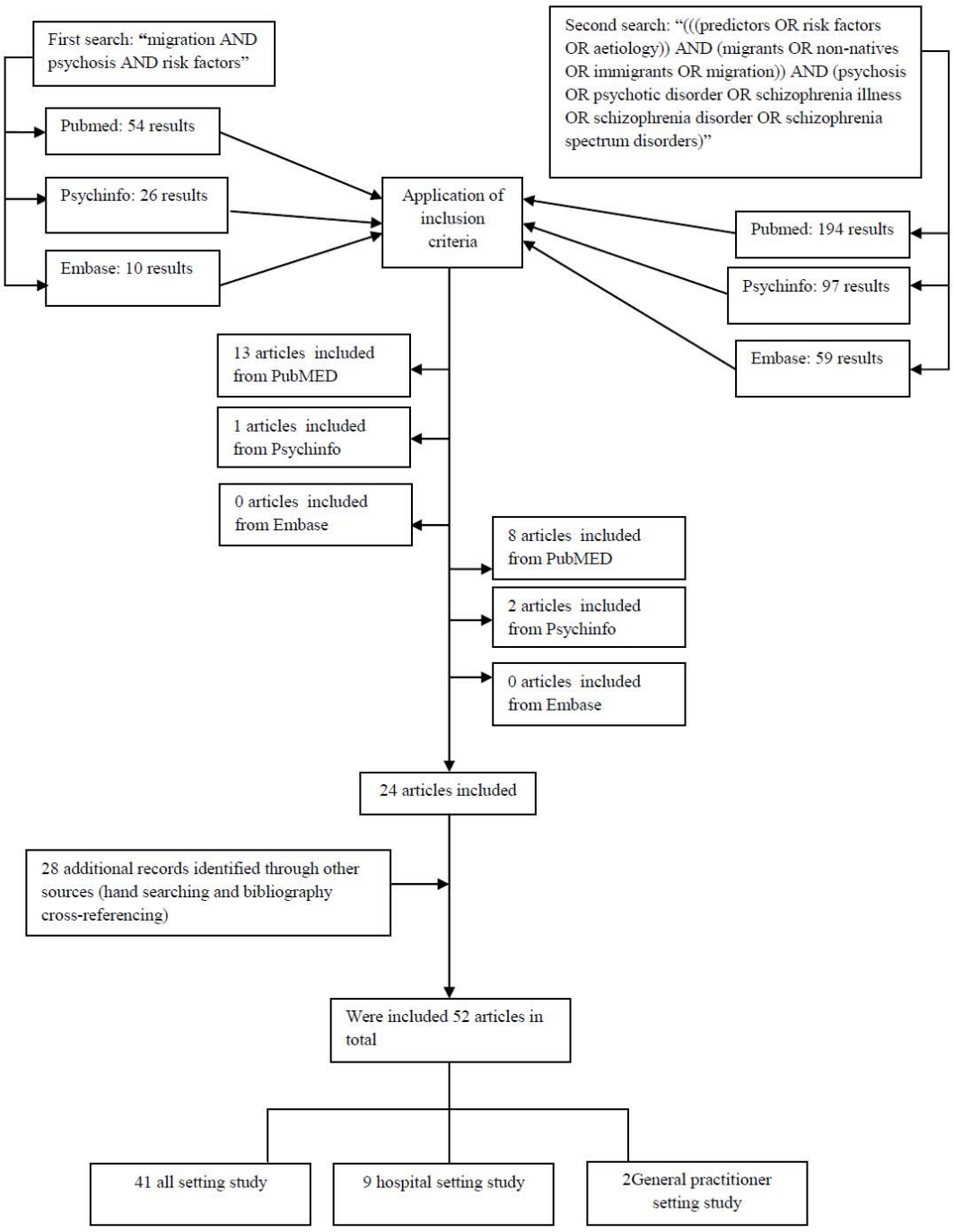

Table 1.1 Characteristics of the included studies (Appendix 1)

1.3.1 UK (27 studies)

The first 2 studies conducted in the UK are retrospective and used data from the Camberwell Register, which recorded all first contact psychiatric patients from Camberwell in south London. Rwegellera et al in 1977 (Rwegellera 1977) found higher rates of schizophrenia in migrants, particularly among West African, and also among West Indian people, compared with native non migrants. Bebbington et al in 1981 (Bebbington et al. 1981) found a higher rate of schizophrenia in West Indians and in Irish women and a relatively low rate in Irish men.

The first population-based study conducted in UK on FEP patients was by Harrison et al (Harrison, Owenset al. 1988) in Nottingham using the 1981 Census and found a strikingly high rate of schizophrenia in African-Caribbean first and second generation compared to the general population. The study by Harrison (Harrison, Glazebrook et al. 1977), carried out in Nottingham on all incident cases of psychosis, was the first study to identify the excess of psychosis among African-Caribbeans (AC) in the UK in both first-and second-generation (RR 8.7, CI 6.1-12.3). This study also made further interesting comparisons between white and AC FEP patients. ACs were more frequently unemployed men and, less frequently qualified professionals. This study also showed that there was a higher consumption of drugs in W patients compared to AC. Finally, they found no differences between AC and W on age at onset and distribution of diagnoses of psychotic spectrum disorders. Cantewell et al (Cantwell,Brewin et al 1988) studied the prevalence of substance misuse in the same FEP incidence cohort and also found that substance misusers where less like to be African-Caribbean.

King et al. (King, Coker et al. 1994) used London data from the population census of 1991 and carried out a prospective study of all ethnic minorities, with the use of research diagnostic interviews. This study found higher rates of psychosis for all ethnic minorities, with a risk of schizophrenia of 3.6 (95% CI, 1.9-7.1) and of non-affective psychosis of 3.7 (95% CI 2.2-6.2) higher compared to the white ethnic majority. The authors of this study argued that their results testifies in favour of strong “push” environmental factors in the

development of psychosis in all migrants groups. The study also identified a higher prevalence of "atypical psychoses" (characterized by a preponderance of the women, a rapid onset, prominent emotional symptoms, and florid delusions, often religious). The frequency of these atypical psychotic syndromes, especially in African-Caribbean first generation migrants, had been observed previously in clinical studies (Littlewood and Lipsedge 1981)].

Coid et al., in 2008 (Coid, Kirkbride et al. 2008) analysed 484 patients who presented over a period of 2 years, in three districts of east London. They stressed that the risk of psychosis remained the same between the first and second generations of the same ethnicity, but was different between the ethnic groups. Some 15 years later then, this study reached the opposite conclusion with respect to those of King et. al in '94 (King and Coker 1994). This may indicate that the socio-environmental risk factors operate differently in different ethnic groups, but not according to the state of migration, both because some ethnic groups are more likely to experience discrimination, and because other ethnic groups such as Asians, have more resources to cope with adversity such as greater support and social cohesion.

The first case-control population-based study was by Bhugra et al (Bhugra,, Leff et al., 1997): the study evaluated all cases of psychosis in the period 1991-1993 in the health districts of Camberwell in South London and Ealing East London. This study found that AC is the ethnic minority at greatest risk and that this ethnic group was particularly burdened by unemployment much more frequently than Asian and W minority groups. Thus, unemployment is an important candidate to explain the excess of psychosis seen in the AC minority. Asians were older at onset and more often married and born overseas, compared to BC and to W.

Mallet, et al (Mallett, Leff et al., 2002; , Mallett, Leff et al., 2004] later reported further case-control analyses on the same sample and showed AC patients had undergone separation from parents more frequently, both compared to controls and other ethnic groups. According to the authors, it is important to understand whether this is a characteristic related to the migration process or a consequence of the failed integration process. These authors also found that unemployment and low education were significantly more frequent in AC cases compared to controls of the same ethnic group and also to cases

belonging to other ethnic groups (white and other minorities). These findings were crucial to further development of the social developmental hypothesis to explain the excess of psychosis found in AC group.

Bhugra et al in 2010 (Bhugra,, Leff et al., 2010) applied the Culture Identity Schedule on the same sample of their previous study (Bhugra, Leff et al., 1997) They interestingly found that African Caribbean patients were significantly less traditional than their controls in their use of language, gender roles, and contact with relatives, desire to live and work with white people. Patients of Asian origin were not found to be different to their controls about their traditional values. Paradoxically, AC patients were those more frequently unemployed and less likely to own their own home compared to the other ethnic minorities group. The authors conclude that the difference found between the 2 groups of patients supports the hypothesis that vulnerable AC may be more prone to schizophrenia because their frustrated attempts to integrate into white society leave them marginalized and distanced from the support offered by other members of their ethnic group.

The first results of the important British study AESOP were published in 2006 (Morgan, Dazzan et al. 2006). This is an incidence and case-control "population based" study, conducted in the UK over a period of three years (from September 1997 to August 2000). This multicentre (Nottingham, Bristol, South-East London) study, involved all people aged 16 to 65 who had a first psychotic episode (F10-29, F30-33) during the study period. This study found that incidence rates of psychosis were higher in some ethnic groups (African-Caribbeans and Africans have a much higher risk compared to others) (Fearon, Kirkbride et al., 2006). The factors highlighted by the AESOP study as possible candidates for the excess of psychosis in migrants and particularly in those groups at higher risk were: death or separation from parents before the age of 16 years (a situation that has been found to occur most frequently in AC, control and cases) (Morgan, Kirkbride et al., 2007); social isolation, social disadvantage, (Morgan, Kirkbride et al. 2008) and the perception of social disadvantage (Cooper ,Morgan et al. 2008); the "mismatch" between expectations and achievements (Reininghaus, Morgan et al., 2008); strong cultural identity (as a dimension which exacerbates the distance between minorities and majorities and that were found more frequently in ethnic minorities cases, rather than in the controls) (Reininghaus, Craig et al., 2010).

Two studies conducted using the AESOP samples investigated minor physical anomalies (Dean, Dazzan et al., 2007) and neurological abnormalities (Dazzan, Lloyd et al. 2008) across ethnic groups and found a higher prevalence of those factors in cases of all ethnic groups, compared with controls, without any differences in the magnitude of the association between ethnic groups. Finally, the study by Morgan et al (Morgan, Dazzan et al. 20108) greater differences in brain structure between black patients compared to black controls (such as reduced global gray matter and increased gyros gray matter) than between white patients compared to white controls. The authors conclude that explaining theses findings is at best speculative because they could be related to exposure to more early neurological insults, but also they could be consequences of greater exposure to adversity and trauma or to different exposure to antipsychotic (notably the current dosage of antipsychotic medication was significantly higher in the black Caribbean and black African patients).

The study by Boydell et al. (Boydell, van Os et al 2001) is to our knowledge the first study to evaluate variables of context. This historical cohort study (1988-97) carried out in South London (2001) highlighted a "dose response" variation of incidence of psychosis to the ethnic minority density in the area. The relative risk of psychosis for minorities who live in areas with low ethnic density (less than 22%) was about twice(RR 4.4) the risk for those living in areas of high density (RR 2.4). According to the authors, this finding may indirectly confirm the epidemiological importance of social networks in protecting individuals from stress factors that can contribute to psychosis onset.

Later, several studies have evaluated the effect of neighbourhood variables, showing that the incidence of schizophrenia is heterogeneous among places (Kirkbride, Fearon et al. 2006) and lower in areas where white British and ethnic minority groups live in more cohesive and less fragmented milieu (Kirkbride, Morgan et al. 2007). The authors of this latter study conclude that the variance in the incidence of psychosis in South East London cannot be explained only on the basis of individual variables such as age, gender and ethnicity; socio-environmental risk factors measured at the level of neighbourhood (such as voter turnout, ethnic density, ethnic fragmentation, and socio-economic deprivation) may help to explain this heterogeneity. One hypothesis is that social capital may mediate the effect of these variables, in agreement with the hypothesis of Faris and

Dunham (Faris and Dunham et al. 1939) (the highest rates of schizophrenia were in more disorganized cities, not necessarily in the poorest). Later Kirkbride et al (Kirkbride, Boydell et al. 2008) found that there is not linear association between the level of social cohesion and trust (SC & T) at the neighbourhood level and the incidence of schizophrenia: the neighbourhood with low and high levels of SC&T had significantly increased rates of schizophrenia compared with median neighbourhood. One hypothesis to explain these findings is that residents living in high social capital areas were excluded from access to that social capital; living in neighbourhood where someone is perceived as an outsider may compound the psychosis risk. Cheng in 2011 (Cheng, Kirkbride et al. 2011), in a study of 285 cases with a psychotic disorder, note that ethnicity seems to have a role in modifying the risk of the already known differences between urban and rural settings. Black ethnicity was associated with a higher incidence of psychosis compared to white British (IRR 2.1, 95% CI1.1-3.8); no other ethnic group was observed to have elevated rates of psychosis. Recently, Schofield et al. (Schofield, Ashworth et al., 2011) conducted a retrospective study using general practitioners records and found a higher incidence rate of psychosis in black patients compared with white but not in the higher ethnic density area in Lambeth (south London). Interestingly the authors found the effect of social deprivation was lower than that of ethnic density.

1.3.2 The Netherlands (10 studies)

Selten et al conducted the first study in The Netherlands (Selten, Slaets et al. 1997) aiming to compare the risk of a first admission for schizophrenia for Surinamese- and Dutch Antillean-born persons aged 15-39 years to that for their Dutch-born peers in the period 1983-1992 and found the risk for the immigrants was three to four times higher than that for the Dutch-born. The age-adjusted relative risks were as much increased in Surinamese immigrants as in Dutch Antilleans. These results remained essentially unchanged when the type of schizophrenia (`broad' or ` restricted ') and the required number of hospitalizations (at least one or two) were considered. Interestingly, the age-adjusted relative risks were significantly higher for male than for female immigrants.

Again Selten et al. (Selten, Veen et al., 2001) conducted a prospective study based on GP records and found that the risk of schizophrenia and other psychotic disorders was higher in several but not all immigrant groups. The risk was particularly high in first and

second generation immigrants from Morocco. A different risk in different ethnic groups was confirmed also by a subsequent study conducted by Selten et al. (Selten, Cantor-Graae et al., 2002) using a hospital admissions registry: they found an increased risk of hospitalization in immigrants from the Dutch Antilles but not from Surinam and an increased risk in younger men from Morocco and Turkey (but not in women and in older immigrants from those countries). These results were confirmed by Veling and colleagues in 2006 (Veling, Selten et al. 2006): this study revealed an increased risk of psychosis for immigrants of all ethnic minorities, in particular for the second generation migrants. This study also found a gender difference: first and second generation men from Morocco showed increased risk of psychosis compared to natives, while this increase is not found in women. An important difference with the British studies, is that migrants at highest risk are not black (Surinamese and Antillean migrants), but those more recently emigrated from Morocco. The authors comment that immigrants from Morocco have a more difficult post-migration adjustment, with high stress of acculturation, which, following the hypothesis of Berry et al. (Berry, YHP et al. 2002) could play an important role in the beginning of psychosis in this group.

In 2007, Veling et al. (Veling, Selten et al. 2007), found that across ethnic minorities the incidence of schizophrenic disorders increased with the degree of perceived discrimination. However, in a subsequent study (Veling, Hoek et al. 2008) Veling et al did not find a different prevalence of perceived discrimination in the year prior to illness onset between cases and controls.

In 2008, Veling and colleagues (Veling, Susser et al., 2008) showed that the increased risk of psychosis in ethnic minorities was significant in low-density ethnic area, but not in those with higher density and concluded similarly to AESOP study (Kirkbride, Morgan et al. 2007) on the hypothetical role of social networks and social capital in the development of psychosis.

Finally in 2011 Veling et al. (Veling, Hoek et al., 2011) found that younger age at the time of migration predicted a higher risk for psychotic disorders among immigrants in the Netherlands. The authors comment that this is against the selective migration hypothesis, because the risk was most markedly increased among immigrants who did not migrate on their own initiative but were brought to the Netherlands in childhood by their family. It could

be possible to argue against this conclusion on the basis that those families who migrated with their young children might have had fewer ties and higher genetic risk. The stronger argument from this study against the selective migration hypothesis is that the younger age at migration is predictive of the risk to develop psychosis suggesting that duration of exposure is relevant.

Another study conducted in Netherlands in 2008 by Selten et al. (Selten, Blom et al., 2008) addressed the problem of genetic predisposition to psychosis in migrants. The authors of this study administered the Family Interview for Genetic Studies to a sample of Morocco migrants and Dutch natives FEP patients and found the risks for NAPD in both parent groups were similar (age and sex-adjusted odds ratio 1.0; 95% CI: 0.3–3.8). However, among the siblings, the risk for NAPD was significantly higher for the Moroccan-Dutch than for the Dutch (sex-adjusted hazard ratio 4.5; 95% Confidence Interval: 1.5–14.0). This was due to a large number of cases among the brothers of the Moroccan-Dutch patients (N=14), not among their sisters (N=1). Thus, the authors conclude that their preliminary results suggest that environmental factors in the Netherlands have a greater impact on the psychosis risk for male immigrants from Morocco.

1.3.3 Sweden (5 studies)

The first study conducted in Sweden was by Zolkowska et al (Zolkowska, Cantor-Graae et al. 2001), which found a two-timeshigher risk for admission for schizophrenia in migrants compared to natives, particularly among migrants from East Africa. Interestingly, they found a mean length of stay in Sweden prior to the illness onset of 11 years. In 2005 Cantor-Graae et al. (Cantor-Graae and Zolkowska et al. 2005), in Malmo found an increased incidence of psychotic disorders and schizophrenia in first generation immigrants, but not in second generations. They explain the lack of risk in second generation immigrants by the fact that immigrants arrived in Malmo only during the 1990s; thus their offspring are only now approaching early adulthood. The risk was particularly high for immigrants from countries where the majority of the population is “black" and from developing countries. Moreover, they found that over 50% of the first generation immigrants had resided in Sweden for 10 years or more prior to their first contact for psychotic symptoms, suggesting that the risk associated with migration may accumulate over time.

The authors formulated the social defeat hypothesis, which postulates that social defeat stress leads to excess dopamine release or dopaminergic hyperactivity in mesolimbic brain areas. Finally the authors found 3 to 5 years later 25% of patients had different diagnoses as previously; the majority of those patients with diagnostic conversion at follow-up were immigrants. Three more studies were conducted in Sweden but only cover hospitalization records and found higher risk of hospitalization in first generation (Hjern, Wicks et al.,,2004; Sundquist and Frank 2004) as well as in second generation migrants (Hjern and Wicks 2004,, Saraiva Leao, Sundquist et al.2005). Notably, Hjerin et al. (Hjern, Wicks et al., 2004] found higher risk of hospitalization in most immigrant groups but not in migrants form west European countries and that the risk was strongly reduced after adjusting for socioeconomic indicators.

1.3.4 Denmark (5 studies)

The first study in Denmark was conducted by Mortensen et al. ([Mortensen, Cantor-Graae et al., 1997) over hospital admission records and found a higher RR for schizophrenia and non affective but not for affective psychosis among immigrants. Cantor-Graae et conducted 2 cohort studies (Cantor-Graae, Pedersen et al. 2003; , Cantor-Graae and Pedersen 2007).. In both studies the authors used the Danish Civil Registration System. In the first study (Cantor-Graae, Pedersen et al. 2003), which primarily concerns people resident in Denmark by their 15th birthday, the authors found an increased risk of schizophrenia in first and second generation migrants. Notably they found an increased risk of developing schizophrenia also among people with a Danish background who had a history of foreign residence prior to their fifteenth birthday. Thus the authors conclude that migration *per se* might be a more important component in the migrant effect than ethnicity. They also found significant variation in risk magnitude across regions of birth. In the second study (Cantor-Graae and Pedersen 2007) focusing on the second generation, Cantor-Graae et al found the increased risk of schizophrenia in second-generation immigrants remained constant over time, despite social and environmental changes in Denmark during the study period. The risk of schizophrenia among second-generation immigrants was substantially increased when both parents were foreign-born, suggesting that dual foreign born parentage represents an increased parental disadvantage. Moreover, the RR of

schizophrenia for second generation migrants was significant after adjustment for a number of potential confounders; family member residing abroad at the time of the child's 15th birthday, change of residence during upbringing, parental age at child's birth, history of mental illness in parent or sibling, the degree of urbanization at birth and during upbringing in Denmark. Furthermore, they found that second generation migrants with one migrant parent and one native parent are more susceptible to the urbanicity effect, while the second generation with two migrant parents have lower rates. Thus, the authors write "the more 'Danish' the family is, the greater is the urbanization effect" and "Urban-born second-generation immigrants by both parents, that is individuals having maximum exposure to both risk factors, showed no evidence that their dual exposure resulted in substantially greater risks of developing schizophrenia with increasing levels of urbanization" (Cantor Graee.& Pedersen, 2007). .

They also found that parental region of origin is more important for the second-generation effect than the developmental level of the country. Finally they also confirmed the greater risk of schizophrenia when a family member was living abroad and for a personal history of living abroad. Thus period of emigration, or the emigration process, may confer an increased risk for schizophrenia regardless of whether the parents are foreign-born or natives Danes.

In 2009 Norredam et al (Norredam, Garcia-Lopez et al. 2009) found a higher risk of having a first time contact for a psychotic disorder for all refugees compared to native Danes, particularly for East Europe refugees.

Finally, Cantor-Graee and Pedersen (Cantor Graee.& Pedersen, 2007) examined the full range of psychiatric disorders associated with any type of foreign migration background among persons residing in Denmark, including foreign-born adoptees, first- and second-generation immigrants, native Danes with a history of foreign residence, and persons born abroad to Danish expatriates. They found that all categories of foreign migration background, except persons born abroad to Danish expatriates, were associated with increased risk for at least 1 psychiatric disorder. They confirm the 2-fold risk for developing schizophrenia and schizophrenia spectrum disorders for first- and second generation immigrants in Denmark. In particular, first- and second-generation immigrants having 2 foreign-born parents showed significantly elevated IRRs solely for schizophrenia

and schizophrenia spectrum disorders. The authors hypothesized that persons having 2 foreign-born parents may have greater visibility than persons having mixed parentage because of greater differences in physical or behavioral characteristics and might be particularly vulnerable to chronic social defeat. Therefore, some migrants may be especially challenged by their greater visibility or "otherness" in Danish society. They comment that it cannot be ruled out that their risks for less severe psychiatric disorders may have been underestimated.

Another very important result of this study is that the migrant group most at risk of developing mental illness is constituted by foreign-born adoptees. This group of people could represent "the extreme" of the migration dimension within the psychosis risk-perspective and to be foreign born adopted could mean to have been exposed in a stronger way to all the social and environmental factors which could make migrants particularly vulnerable to psychosis, such as separation from parents and early age of migration.

1.3.5 Italy (1 study)

In Italy our previous study showed a higher incidence rate of psychosis among migrants compared to natives (Tarricone, Rossi et al, 2012).Migrants have been found to be more often married and living outside the family of origin, while they showed a lower substance abuse rate compared to natives. We hypothesised that these factors could underlie a lower degree of biological vulnerability and, perhaps, a higher burden of disadvantages and other environmental risk factors in migrants compared to natives.

2.3.6 Non European Countries (7 studies)

Only 7 studies were found that were conducted outside Europe: namely 2 in Canada (Bland and Orn 1981; Smith, Boydell et al. 2006), 2 in Israel (Corcoran, Perrin et al. 2009, Werbeloff, Levine et al. 2012) and 3 in US (Schaefer, Brown, et al 2000; Bresnahan, Begg et al. 2007; Brown, Bottiglieri et al., 2007) The first study conducted in Israel is a population based research cohort study known as the "Jerusalem Perinatal Study" (Corcoran, Perrin et al. 2009).This study did not find any change in risk of schizophrenia for offspring of immigrants, including those who had only 1 immigrant parent and those who had 2 immigrants' parents. The second one, conducted by Werbeloff et al in 2012 (Werbeloff, Levine et al. 2012) using psychiatric hospitalization records found a significantly greater risk

of hospitalization for many immigrants groups, overall for women belonging to Middle East, Far East , Eastern Europe, Caribbean and South America groups. Interestingly this study also found that people who migrated prior to the age of 15 were at greater risk of schizophrenia, particularly those from Far Eastern and Caribbean and South American countries.

The study conducted in Canada by Bland et Orn in 1981 (Bland and Orn 1981) found that immigrants from Eastern Europe and immigrants speaking a minority language were at high risk of admission for schizophrenia. Later, in 2006 Smith et al. (Smith, Boydell et al. 2006) found incidence increased over time by 1913 in the immigrant but not the Canadian-born population. The authors discussed that the era included in the study saw a rapidly expanding economy followed by a recession with increasing unemployment and intolerance of immigrants. These social changes coincide with an increasing incidence of schizophrenia in immigrants but not in the Canadian-born population. This finding is in agreement with those of recent studies in suggesting that social and economic adversity may influence the level of risk for schizophrenia in migrants.

In the US several interesting cohort studies have been conducted. The Prenatal Determinants of Schizophrenia (PDS) birth cohort was established in a fully insured, urban born population, with comprehensive assessments at pregnancy and birth. It derives from the large birth cohort assembled in the Child Health and Development Study (CHDS) to investigate factors affecting pregnancy outcomes and child development. This cohort provided a unique opportunity to examine race and risk of schizophrenia apart from the influence of gross disparities in health care access and socio-economic circumstances in the family of origin. The study by Bresnahan et al (Bresnahan, Begg et al. 2007) found African Americans were about 3-fold more likely than whites to be diagnosed with schizophrenia in comparison with whites in this birth cohort. The authors also found that this association may have been partly but not wholly mediated by an effect of race on family socio-economic circumstances. Several other studies conducted on the PDS cohort found interesting correlations between prenatal exposures such as high maternal BMI and elevated prenatal homocysteine levels and future development of schizophrenia and related disorders in the offspring (Schaefer, Brown, et al 2000; Brown, Bottiglieri et al., 2007).

These studies found that ethnicity had no appreciable effects on the association between those factors and risk of schizophrenia.

1.4 Discussion

The studies reviewed cover a period of more than 30 years and agree in highlighting an increased risk of psychosis in some immigrants, but not all. The higher incidence of psychosis has been found in first as well in second generation migrants, with the exception of the study in Malmo, where only first generation migrants have been found at higher risk. As the authors comment, this discrepancy is probably due to the fact that in Sweden migration is a recent phenomenon that began in the 90's. In 2005, when the study was conducted, the second generation migrants were too young to be at risk of psychosis.

During the 30 years that these studies have been conducted there has been a major demographic change in populations of these countries, an aging migrant population and hence a change in the risk of psychosis. In the meta-analysis of Cantor-Graae& Selten (Cantor-Graae and Selten, 2005) the relative risk of developing schizophrenia for the first-generation immigrants is 2.9 and increased to 4.5 for second generation immigrants. Risk of psychosis in second generation has been reduced in recent meta-analysis of Bourque et al (Bourque, van der Ven et al. 2011), which showed similar risk between the first (OR 2.3) and second generations (OR 2.1) migrants.

The literature review has found, as already reported by Morgan & Fearon (Morgan and Fearon 2007), that there are very few studies that have focused on specific risk factors of psychosis in migrants. The large majority of these studies were conducted in Northern Europe, specifically in the UK, Holland, Denmark and Sweden and are focused primarily on post migration factors.

The review has sought to answer the following questions :

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1.4.1 **The risk of psychosis varies depending on migrants-geographical origin and the host country?**

All the studies reviewed, except one of the oldest that of King (King, Coker et al., 1994), reveal a different risk depending on the ethnic minority and / or geographical origin of the first and second generation migrants. As already showed by Borque et al., (Bourque, van der Ven et al. 2011) it is interesting to note that the risk group varies in different countries: In the UK, studies agree in identifying a higher risk in black minority groups, particularly in Black Caribbean; in the Netherlands, North Africans have a higher risk. Thus, it's very intriguing to understand what are those characteristics of each specific host society that interact with each specific type of migrants and ethnic minorities (first-or next-generation; economic migrants or political migrants, etc.) to increase the risk of psychoses. It seems necessary to look for the risk of psychosis in the "immigrant status" rather than in the "migrants": "immigrant status" signifies the special meeting between the migrant and the welcome- country. The nature of this meeting is particular and could explain the variation of psychosis risk for different groups of migrants in different countries.

The following tables (1.2, 1.3, 1.4, 1.5) show the range of risk factors investigated as putative explanations for the phenomena:

Table 1. 2 Risk Factors for FEP in migrants

	Evidence	**Studies (AS= all setting; H= hospital record; GP= general practitioner)**
Pre Migration Phase		
Individual level		
Selective migration	no	Selten et al, 2002 (H)
Genetic	no	Selten et al, 2008 (AS)
Neurological markers	no no	Dazzan et al, 2008 Dean et al, 2007
Area level		
Degree of development of country of origin	yes	Cantor-Graae 2005(AS)
Migration Phase		
Reason for migration: refugees	Yes yes	Norrendam 2009(H) Sundquist 2004 (H)
Early age of migration	Yes Yes yes	Veling 2011(AS) Harrison 1988(AS) Werbeloff 2012(H)
Past history of migration before age of 15	yes	Cantoor-Graae 2003(AS)
Post Migration phase		
Individual level		
Prenatal Determinant (II generation) • Homocysteine levels • Maternal BMI	 No No	 Brown 2007 (AS) Schaefer 2000(AS)
Parental separation before age 16	Yes Yes	Morgan 2007(AS) Mallet 2002 (only AC) (AS)
Unemployment	Yes Yes Yes yes	Reininghaus 2008(AS) Mallet 2004(AS) Mallet 2002(AS) Bhugra 1997(AS)
Living condition • Far from family • alone	 Yes yes	 Cantoor-Graae 2007(AS) Mallet 2004(AS)

Low employment level	yes	Bebbington 1981(AS)
Low education	yes	Mallet 2004(AS)
Substance abuse	no	Harrison 1997(AS) Tarricone 2012 (AS)
Skin colour	yes	Cantoor-Graae 2005(AS)
Loss of Cultural Identity	yes	Reininghaus 2010(AS) Bhugra 2010 (only AC)
Perceived discrimination	Yes Yes no	Cooper 2008(AS) Veling 2007(AS) Veling 2008b(GP)
Self-esteem and self-concept	yes	Cooper 2008(AS)
Mismatch between expectation and achievement	Yes yes	Reininghaus 2008(AS) Mallet 2004 (only Indians, no AC; only for housing) (AS)
Social defeat	Yes Yes yes	Morgan 2008(AS) Bresnahan 2007 (AS) Schofield 2001(GP)
Brain structure	yes	Morgan et al., 2009
Area level		
Low ethnic density	Yes Yes Yes yes	Kirkbride 2008(AS) Veling 2008(AS) Kirkbride 2007(AS) Boydell 2001(AS) Schofield 2001(GP)
Economic crisis and intolerance	yes	Smith 2006 (H)

Table 1.3. Ethnicity/country of origin and risk of FEP in migrants

Host Countries	**Ethnicity/country**	**Studies (AS= all setting; H= hospital record; GP= general practitioner)**
UK	Black	Cheng 2011(AS) Reininghaus 2010(AS) Cooper 2008(AS) Kirkbride 2008(AS) Kirkbride 2006(AS) King 1994(AS) Schofield 2001(GP)
	African-Caribbean	Reininghaus 2008(AS) Harrison 1997(AS) Bhugra 1997 (AS) Harrison 1988(AS) Bebbington 1981(AS)
	African-Caribbean and Africans	Coid 2008(AS) Kirkbride 2007(AS) Morgan 2006(AS) Fearon 2006(AS)
	West Africans	Rwegellera 1977(AS)
	Asians	King 1994(AS)
	Indian	Bebbington 1981(AS)
The Netherlands	Moroccan	Selten 1997(H) Selten 2001 (GP) Selten 2003(H) Veling 2006(AS) Veling 2008a(AS) Veling 2011 (AS)
	The Netherlands Antilles	Selten 2001 (GP) Selten 2003(H) Veling 2008a(AS)
	Surinamese	Selten 2001 (GP) Veling 2006(AS) Veling 2008a(AS)
	Turks	Selten 2003(H) Veling 2008a(AS)
	Other non western countries	Selten 2001 (GP)
Sweden	East African	Zolkowska 2001(AS)

Denmark	European and Scandinavian	Mortesen 1997(H)
Israel	Far Eastern	Werbeloff 2012(H)
Canada	East European	Bland 1981(H)

Table 1. 4. Ethnicity/country of origin and risk of FEP in second generation's migrants		
Host Countries	**Ethnicity/country**	**Studies (AS= all setting; H= hospital record; GP= general practitioner)**
UK	African-Caribbean	Coid 2008(AS) Harrison 1997(AS) King 1994(AS) Harrison 1988(AS)
The Netherlands	Moroccan	Selten 2001(GP) Veling 2006(AS) Veling 2011(AS)
	The Netherlands Antilles	Veling 2006(AS) Veling 2011(AS
	Surinamese	Selten 2001(GP) Veling 2011(AS
	Turks	Veling 2006(AS) Veling 2011(AS
Denmark	Greenland	Cantoor-Graae 2007(AS) Cantor-Graae 2003(AS)
Sweden	Finnish	Leao 2005(H)

Table 1. 5. Gender and risk of FEP in migrants		
Host Countries	**Gender**	**Studies (AS= all setting; H= hospital record; GP= general practitioner)**
Denmark	Male	Cantor Graee & Pedersen 2013 (AS)
Israel	Female	Werbeloff 2012(H)
UK	Black Female African-Caribbean Female under 30	Cheng 2011(AS) Bhugra 1997(AS)
	African-Caribbean Male	Bhugra 1997(AS)
	Asian Female	Bhugra 1997(over 30) (AS) Coid 2008(AS)
	Indian Female	Bebbington 1981(AS)
The Netherlands	Moroccan male	Selten 2003 (H) Veling 2006(AS)
	Surinamese Female	Veling 2006(AS)
	Turks	Selten 2003 (H)

1.4.2 The risk of psychosis varies depending on the migratory history?

Only studies conducted in Denmark (Cantor-Graae, Pedersen et al. 2003; , Cantor-Graae and Pedersen 2007, Cantor-Graae and Pedersen 2013) take into account the migration experience. These studies shows that having had an experience of a foreign residence before age 15 or having a parent with a history of foreign residence before the age 15 of the child are two situations that increase the risk of psychosis, regardless of 'being born in Denmark'. Thus the authors conclude that *migration per se* might be a more important component in the migrant effect than ethnicity. Recently in Netherlands Veling et

al (Veling, Hoek et al. 2011) showed that younger age at the time of migration predicts a higher risk for psychotic disorders and this is further evidence that selective migration cannot explain the higher risk found among migrants. Two studies conducted in Sweden (Zolkowska, Cantor-Graae et al. 2001, Cantor-Graae, Zolkowska et al. 2005) found that the first generation immigrants had resided in Sweden for around 10 years prior to their first contact for psychotic symptoms, suggesting the risk associated with migration may accumulate over time.

1.4. 3. What are the known risk factors for psychosis in migrants?

As summarized in Table 2.2, only a few studies take into account potential risk factors that may affect the pre-migratory phase, migration and the stress of the migration process itself. As already noted by Morgan (Morgan, Charalambides et al. 2010), most of the available studies, lie in the post-migratory phase. The risk factor most commonly investigated by the studies and which shows a degree of cross-cultural consistency is ethnic density: both in the UK and Holland immigrants who live in areas with low ethnic density and are therefore exposed to conditions of low social capital and greater isolation have a higher risk of psychosis. Interestingly, this risk factor at the area level corresponds to an individual risk factor, the strong cultural identity, as a dimension which is exacerbating the distance between minorities and majorities and that were found more frequent in ethnic minorities cases, rather than in the controls (Reininghaus, Craig et al. 2010). Moreover, Cantor Graae and Pedersen (Cantor-Graae, Pedersen 2007] found in Denmark that risk of schizophrenia among second-generation immigrants was substantially increased when both parents were foreign-born, suggesting that dual foreign born parentage represents an increased parental disadvantage. It is possible to hypothesize that low ethnic density at the area level, dual foreign born parentage as the familial level and strong cultural identity at the individual level are proxies for isolation of minorities compared to the native majority. The risk factor underlying these conditions could be isolation, which, as has already been pointed out, could lead to dopaminergic dysfunction. The Aesop study showed that social isolation and social disadvantage are more frequent in FEP migrants compared to FEP white majorities (Morgan, Kirkbride et al. 2008).

Other social and psychological risk factors in migrants highlighted by the studies reviewed are the perception of social disadvantage and discrimination found in UK by

AESOP study (Cooper, Morgan et al. 2008) as well as in the Netherlands (Veling, Selten et al. 2006) and "mismatch" between expectations and achievements (Reininghaus , Morgan et al., 2008).

Chapter 2: Aims, Hypotheses and Position taken

My PhD project aimed to : 1) Verify whether there was an excess of psychosis among migrants in Italy and whether this applied to internal migrants as well as to migrants from outside Italy 2) Further understand the role of known environmental risk factors for psychosis (substance use, to be single/living alone, to be unemployed and low level of education) in the development of psychosis .

I hypothesized that :

- first generation external migrants are at higher risk of psychosis also in Italy;
- first generation internal migrants also have an higher incidence of psychsosis
- first generation migrants have no clinical differences, but better social functioning and better social outcomes comapred to natives

Posiition taken

One interesting result of the recent meta-analys of Bourque et al., (Bourque, van der Ven et al. 2011) is that.the incidence rate ratio for first generation migrants at whole considered (with-out ethnic subgrouping) to develop psychosis is similar among studies conducted in different countries, even if incidence rate variation has been observed among coutries. Generally migrants have twice the risk of natives to develop psychosis. This could reflect a model that we can define as “history of migration times environment”. My position is that history of migration and not genetic/ethnic or socio-economic characteristics puts migrant people at higher risk to develop psychosis compared to natives.

I also postulate that migrants have more “exogenous” causation of psychosis, related to the difficult process of migration itself, compared to natives. This could imply better social outcomes compared to natives, even if they do not have clinical different presentation and early illness course compared to natives.

Chapter 3: Methodology

3.1 Study Design : The Bologna First Episode Psychosis Study

The Bologna First Episode Psychosis Study (BoFEP Study) is an on-going incidence study of first episode psychosis cases conducted since January 2002 in the 3 Community Mental Health Centres (CMHCs) covering the West Bologna population (CMHCs Nani, Scalo and Tiarini). In the Bologna West CMHC special FEP programmes have been in place for several years; in particular a consultation-liaison programme with general practitioners (GPs) and other agencies was developed in late '90s to facilitate better identification of FEP cases (Berardi et al., 1999).

The study catchment area (West Bologna) was defined in terms of the Census Area covered by participating mental health services. The Bologna West catchment area includes around half the total Bologna inhabitants. Denominators for the population at risk of psychosis were derived for each year from the Municipality Registry [mid period population, 2006 year: 114,993 inhabitants: 67,887 (59.1%) natives, 31,448 (27.4%) internal migrants (of whom 25,247, 80%, from South Italy) and 15,568 (13.5%) external migrants].The West Bologna area is exclusively urban, according to the UN criteria (United Nations, 1980). Bologna has a population density of 2,671.3 inhabitants per kmq.

3.2 Inclusion and exclusion Criteria

The BoFEP study includes an assessment of all new cases of psychosis at their first contact with CMHC and after 3 and 12 months..

Patients between 18 and 64 years old with a first episode of psychosis (psychotic coding F10–F29 and F30–F33 in ICD-10) were identified among those presenting for the first time to the three CMHCs within tightly defined catchment areas in West –Bologna, Italy over 9 years period (Jenuary 2002 – December 2010). The inclusion criteria are based on those used in the WHO study (Jablensky et al, 1992): i.e., presence of hallucinations, delusions, thought disorder, bizarre or disturbed behaviour, negative symptoms, mania, or clinical suspicion of psychosis; absence of an organic cause or profound learning disability; and no previous contact with psychiatric services for psychotic symptoms.

3.3 Data Collection

A team of researchers was involved in checking weekly all patient contacts with the 3 CMHCs (Nani, Scalo and Tiarini) in the Bologna West Catchment Area. In Italy, CMHCs are services devoted to treating severe mental disorders and in Bologna Mental Health Department (MHD) almost all the patients with FEP are referred to CMHCs. Patients can be referred by many different agencies (GPs, general hospital, social services, police, voluntary organisations, etc) and self-referred. There were regular training events for staff. Each patient meeting inclusion criteria for the study was approached and informed consent sought. Based on the methods used by Cooper et al. (1987), we conducted a leakage study after the survey period to identify any subjects missed by checking the list of patients recorded at the Bologna MHD in the study areas and reviewed all new mental health service registration forms held in the Bologna MHD, and checked computerized information systems. Case notes were used to complete the Item Group Checklist (IGC), part of the SCAN (Schedule for Clinical Assessment of Neuropsychiatry, Version 2.1, World Health Organization-Division of Mental Health, Geneva 1998), to collect symptom-related data at the time of presentation and one month later to ensure that cases met ICD-10 criteria for psychotic disorders. Diagnoses were allocated by consensus agreement from a panel of psychiatrists at each study centre, including myself (the principal investigator) and the clinical researcher who completed the ICG-SCAN. For the analyses, we considered 5 diagnostic groups: 1) all psychoses, 2) affective psychoses (ICD F30-F33), 3) non-affective psychoses (ICD10 F20-29), 4) substance-induced psychoses (SIPs) (ICD10 F10-F19). Diagnostic group 3 non-affective psychosis was divided into 3a) schizophrenia (ICD10 F20) and schizoaffective disorder F25), and 3b) other non-affective psychoses.

We coded ethnicity along with place of birth of the patient and his/her parents. We divided population into three groups: Native in Emilia Romagna (Northen Italy), Internal migrants (from other Italian regions, mainly Southern Italy) and External migrants (from other countries), using the Municipality Registry. In assigning patients to ethnic groups and in collecting other socio-demographic (age, marital status, education, housing, occupational status) and migration history information (birth origin, reason for migration, length of stay in Italy) we used a form developed specifically for the study (Bologna Migration History and Social Integration Interview). Age of onset was collected by asking the patients and/or key informants

about when s/he experienced the first psychotic symptoms as defined above. Date of first contact with services was defined as the date when he/she was referred for the first time to Bologna West CMHC for his/her first episode of psychosis.

3.4 Statistical Analyses

Both the population at risk and the cases of FEP were stratified by gender, age groups of ten years and ethnicity. With regard to ethnicity there were three distinct groups: the natives, that is, people born in Emilia Romagna (Northern Italy); the internal migrants, that is, people born in other regions of Italy (mostly Southern Italy) and migrated to Emilia Romagna; the external migrants, that is, people born abroad and immigrated in Italy.

The strategy of analysis is described in each chapter but in summary :

1. In study 1**(First Episode Psychosis at the Bologna West Community Mental Health Centre: results of an eight-year prospective study)** median incidence rates (IR) with interquartile range (IQR) and incidence rate ratios (IRR) with 95% confidence interval (CI) were calculated. Rates are presented per 100,000 inhabitants at risk per year. Data were analysed by SAS 9.1.3 for Windows.

2. In study 2 (**Risk of psychosis in internal migrants in Italy: results from the Bologna First Episode Psychosis Study**) the crude incidence rates were calculated for all groups of patients examined: by gender, by age and by migration status. Directly standardized incidence rates, standardized for age and gender were then calculated using the distdze command in Stata 10, with the standard considered as the entire study population. The incidence rates are presented per 100 000 person years. There was overdispersal in the distribution of the cases with the variance considerably greater than the mean. Negative binomial regression was therefore carried out to estimate the effect of migrant group after adjusting for age and gender.

The predictive variables examined in both studies 1 and 2 include gender, age at first contact, marital status, education, occupational status, pathway to care, housing, DUP, diagnosis and substance abuse. Population levels of risk factors stratified by age, gender and migrant group were not available. Therefore the prevalence of the risk factors,

diagnoses and substance misuse were analyzed using one way-Anova test and chi square test to compare categorical and continuous variables between migrants and natives. A multivariable logistic regression model was used in study 1 to analyse the relationship between migration, marital status, pathways to care and duration of untreated psychosis (DUP), after adjusting for all the significant effects identified in univariable analyses. These analyses were done using SPSS for windows Version 14.

In study 3 (**First Episode Psychosis course: results from a 1 year follow-up study in Bologna)** we used univariate analysis (chi square test for categorical data, Fisher's exact test for categorical data with small numbers or Wilcoxon signed rank test for nonparametric data) to study the associations between psychiatric hospitalizations, occupational status at 12 month and baseline variables. These variables were gender, age, place of birth (migration status), marital status, education, housing, occupational status, psychiatric diagnosis, DUP and substance use. In a multivariate logistic regression analysis we adjusted the associations found between substance use and hospitalizations for age, gender and all the statistically significant effects identified in first univariate analysis testing the addition of each factor using the Likelihood Ratio Test. Data were analyzed using SPSS for Windows Version 14.

Chapter 4: Study 1- First-episode psychosis at the West Bologna Community Mental Health Centre: an 8-years prospective study

4.1 Background of the Bologna First Episode Psychosis (Bo-FEP) Study

Before this study was carried out the evidence showing that there are high rates of first episode psychosis (FEP) in immigrant populations were mostly conducted in the UK and Northern Europe. Following the rationale that a significant contribution to our understanding of the major environmental factors behind FEP could come from studies conducted in other parts of the world, the Bologna first episode psychosis study was carried out.

From our clinical experience, also in Italy migrants appeared increasingly affected by the onset of a psychotic disorder and requiring treatment for these disorders in psychiatric services. I am particularly interested in the interaction between factors around migration and the reception in the host country in causing the rising of psychosis incidence rate in migrants. Before to study it is necessary to determine whether there is an increased incidence in migrants to Bologna as migration took place under different circumstances than to Northern Europe. Therefore I carried out the first study as a simple comparison of rates between native Italians and migrants from outside Italy.

The first study I present here (Bologna First Episode Psychosis – FEP Bo - Study, Tarricone et al., 2012 [1]) has two aims: a) to provide an introduction to, and an overview of, the design and methods of BoFEP study; and b) to summarise the data collected, focusing on the incidence of FEP and the distribution of several risk factors (e.g age, ethnicity, substance abuse) in the sample.

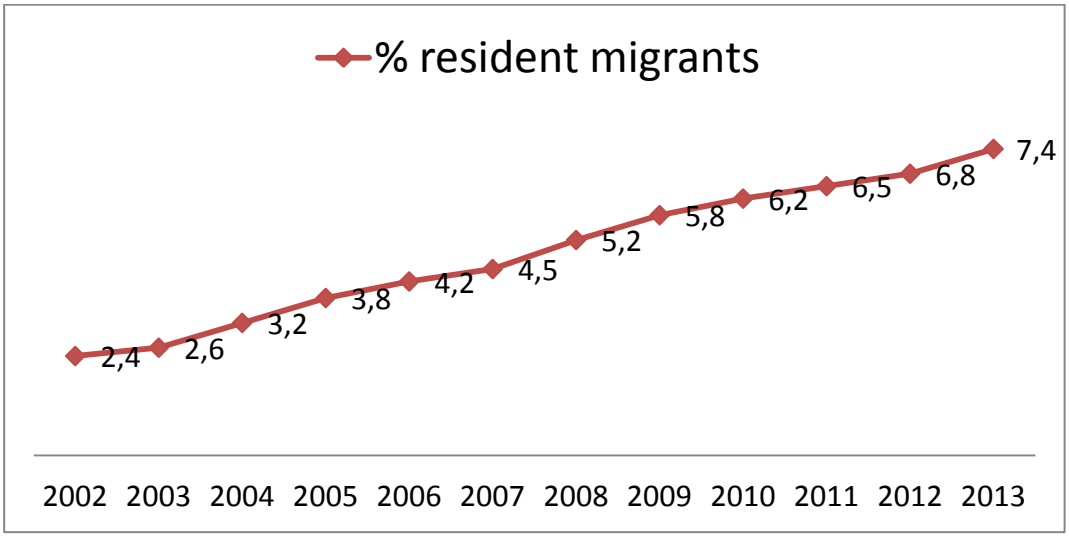
Before introducing the BoFEP study , I briefly describe the migration phenomenon in Italy and particularly in Bologna

[1] Tarricone I, Mimmi S, Paparelli A, Rossi E, Mori E, Panigada S, Carchia G, Bandieri V, Michetti R, Minenna G, Boydell J, Morgan C, Berardi D. (2012) First-episode psychosis at the West Bologna Community Mental Health Centre: results of an8-year prospective study. Psychol Med. 42(11):2255-64

4.1.1 Migration in Italy

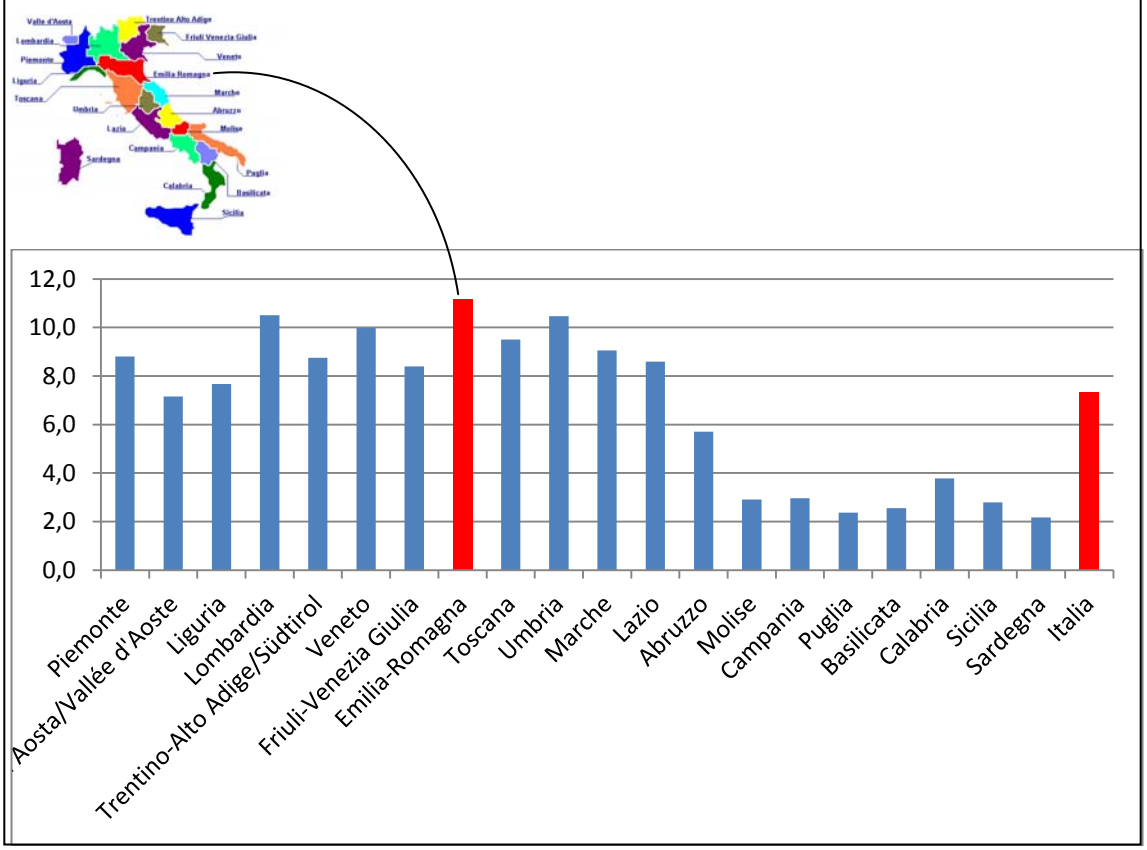
Italy is a country of recent and rapidly increasing immigration (Figure 4.1). Migrants are responsible for a partial demographic balance in Italy, a country struggling with a high and increasing rate of aging, where sixty years old already exceed those under 15 years (Caritas / Migrants, 2010). Despite the political control of migration flows, the increase of foreign residents in Italy was approximately 3 million units in the first decade of this century, during which the foreign presence has almost tripled, and more than 1 million in the last three years (Figure 4. 1). Foreign citizens in early 2013 are almost 4.4 million, 7.4 percent of the total residents: a year before, in early 2012, were 6.8 percent. Compared to 2001, foreigners have more than tripled; in 2012 grew by 8.3 percent (ISTAT, 2014). These figures include children born in Italy to foreign nationals (79,894 ,15% of total births in Italy in 2012), but exclude foreign nationals who have subsequently acquired Italian nationality; this applied to 65,383 people in 2012 . They also exclude illegal immigrants whose numbers are difficult to determine.

Figure 4.1. Resident Migrants in Italy per 100 general population (years 2002-2013 Source of data: Istat, 2014)



The distribution of foreign born population is largely uneven in Italy: 86% of immigrants live in the northern and central parts of the country (the most economically developed areas), while only 14% live in the southern half of the peninsula. The Emilia-Romagna is the Italian region that has the highest incidence of foreigners total residents, with a rate of 11.2% at the 1st January 2013 (compared with a national average of 7.4 %) (Istat, 2014).

Figure 4.2 : Distribution of foreign born population in Italy (% of general population; data from Istat, 2014)



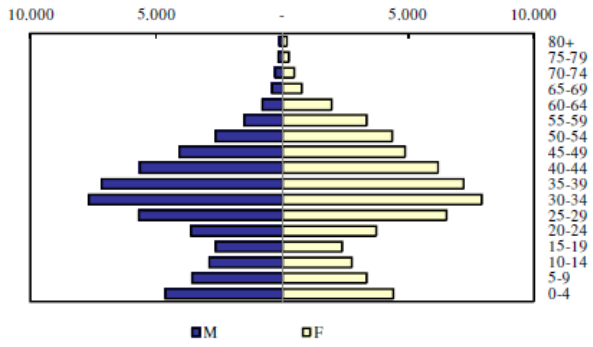
Unlike other European countries such as England and France, where the migration, linked to a colonial past, is a structural component of society for centuries, Italy is faced only recently with the rapid and tumultuous transformation of identity and became from a country of emigration to a country of immigration. According to an anthropological perspective, migration today is largely the result of unbalanced development processes, social injustice and political, economic and cultural neo-colonialism (Mezzadra, 2001; Taliani & Vacchiano, 2006). The undeniable need for labor in our country and in other European countries is related to two aspects of the desertion of low-skilled jobs from the natives and the overall aging of the population, which removes energy production to a system in which the relationship between business and security needs to be properly balanced. The demand for labor is a major pull factor of migration: foreign workers becomes essential in those areas are now "overlooked" by Italian workers, such as domestic work, care for the elderly, agriculture and other strenuous activities and risky (over that little remunerated) such as the building. According to the report statistical Caritas in 2010, at the end of 2009 migrants on

Italian soil accounted for 8.8% of the total population, accounted for 10% of the employees as employees and produced the 11.1% of Gross Domestic Product (Caritas / Migrants, 2010).

4.1.2 The migration phenomenon in Bologna[2]

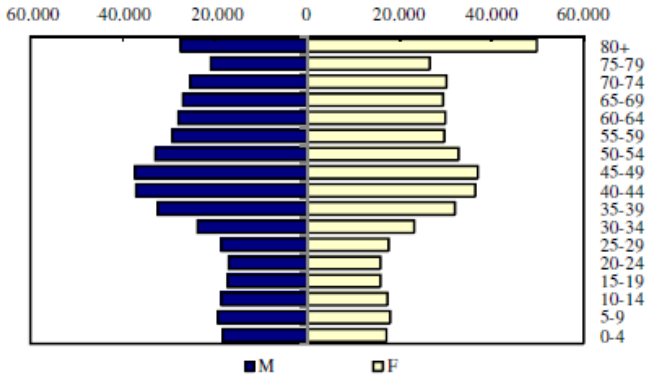
Bologna is the capital of the Emilia Romagna a region of northern Italy. Bologna has 371, 337 inhabitants with a population density of about 2,731 inhabitants per km² . At 1st January 2013, foreigners residing in the municipality of Bologna are 56,155, 14.6% of the total resident population, a rate higher than the regional average (12.2%). Women today are the majority of foreign residents is in the municipality of Bologna, both in the province and regional level. If, in 1992, women constituted just over a foreigner residing on three, starting in 2006 have become more than half, to become 53.2% of immigrants in 2012. The total resident population in Italy has an average age of almost 46 years (45.9). Relevant differences are found between the Italian citizens - with an average age close to 47 years - and foreign population in Italy, with an average of 32.5 years of age. The figure 4.3 shows the age structure of the foreign population resident in the province of Bologna: more than 38% of migrants are in the age groups between 30 and 44 years, followed by those between 15 and 29 years (22, 3%). Even the younger age groups show a considerable weight, with more than a fifth of cases (20.8%) in the age groups up to 14 years. The comparison with the age structure of the Italian population resident in the province of Bologna (Figure 4.4) clearly shows the differences in age structure between the two components of the population.

Figure 4.3 Pyramid of age for the foreign resident population in the province of Bologna. year 2012 (Source: Observatory of Immigration of the Province of Bologna, 2014)



[2] I summarized in this paragraph data from the Research report made by the Foundation Research Institute *Carlo Cattaneo* for the Observatory of Immigration of the Province of Bologna (2014)

Figure 4.4 Pyramid of age for the Italian resident population in the province of Bologna. year 2012 (Source: Observatory of Immigration of the Province of Bologna, 2014)



In Bologna there are foreign citizens from over 145 different countries. The top five nationalities of origin (Romania, Bangladesh, Philippines, Moldova, Morocco) make up about 50% of foreign residents in Bologna. Compared to the provincial and regional level, Bologna has some similarities and some peculiarities. In Bologna, as elsewhere in the region and throughout the country, migrants from Romania are the largest group, and show a very marked increase in the last two years (+ 12.6%). In second place come the migrants from Bangladesh, which show a significant increase (+ 6.1%), so as to have exceeded during the last years Filipino migrants, who are in third place (9.1% of immigrants resident) . At the provincial level, Moroccan migrants are the second largest community and the Albanian group is at 3rd place. In Bologna, as for the rest of the region Emilia Romagna, citizens Moldovans show considerable growth and are in fourth place, ahead of Moroccan migrants and Ukrainians. The Romanian and Moldovan communities are characterized by a predominance of women (55.6% women), while Moroccans and Albanians show a prevalence of the male component.

4.2 Introduction

A systematic review by McGrath et al. (2004a) showed that reported incidence rates of schizophrenia fell within a range of 7.7 to 43.0 per 100,000, with a fivefold variation. Other studies have shown that the incidence is higher among those brought up in urban areas, and that the larger the town, and the longer the individual has lived in the city, the greater the risk (Mortensen et al 1999; Pedersen and Mortensen, 2001). Risk is also elevated among migrant and minority ethnic groups (Cantor-Graae and Selten 2005). The AESOP

(Aetiology and Ethnicity in Schizophrenia and Other Psychoses) study examined both of these effects and found that in the UK the incidence of all psychoses in south-east London was double that in Nottingham and Bristol, and that the incidence in the black Caribbean and black African populations was around 4 to 6 times higher than in the white British population (Fearon et al, 2006). Boydell et al. (2003) further demonstrated that the operationally defined incidence of schizophrenia in South London had doubled between 1965 and 1997 and pointed to migration and drug use as possible contributing factors. Those of black ethnicity were especially vulnerable if relatively isolated in localities where their own ethnic group was in a small minority (Boydell et al, 2003). van Os et al (2010) recently argued that the evidence of substantial variation in the incidence across places and minority groups suggests environmental factors have an important role in the development of psychotic disorders. Given that urbanicity, drug use and migration are increasing in many countries, these reported epidemiological findings are of significant public health importance (Morgan & Hutchinson, 2010). Research that has found associations between psychosis and urbanicity, ethnicity, early trauma, cannabis use, social cohesion and psychotic disorders has been mostly conducted in the UK and northern Europe (Pedersen & Mortensen, 2001; Arseneault et al., 2002;van Os et al., 2002; Cantor-Grae & Selten, 2005; Morgan & Fisher, 2007; Kirkbride et al., 2008; Di Forti et al, 2009). A significant contribution to our understanding of the major environmental factors behind FEP could come from studies conducted in other parts of the world. Our paper has two aims: a) to provide an introduction to, and an overview of, the design and methods of BoFEP study; and b) to summarise the data collected to date, focusing on the incidence of FEP and the distribution of several risk factors (e.g age, ethnicity, substance abuse) in the sample.

4.3 Method

The BoFEP (Bologna First Episode Psychosis) study is an on-going incidence study of first episode psychosis cases conducted since January 2002 in the 3 Community Mental Health Centres (CMHCs) covering the West Bologna population (CMHCs Nani, Scalo and Tiarini). These 3 units constitute the Bologna West CMHC, coordinated by DB. In the Bologna West CMHC special FEP programmes have been in place for several years; in particular a consultation-liaison programme with general practitioners (GPs) and other agencies has

been developed in late '90s and this may facilitate better identification of FEP new cases (Berardi et al., 1999).

The West Bologna area is exclusively urban, according to the UN criteria (United Nations, 1980). The BoFEP study includes an assessment of all new cases of psychosis at their first contact with CMHC and after 3 and 12 months. Following the AESOP Study of Kirkbride and colleagues (2006) we here present data collected during the study period at baseline.

Ethical approval was obtained from the local research ethics committee.

4.3.1 Population at risk

The Bologna West catchment area includes around half the total Bologna inhabitants. The study catchment areas were defined in terms of the Census Area covered by participating mental health services. Denominators for the population at risk of psychosis were derived for each year from the Municipality Registry and ranged from 118,239 in 2002 to 116,499 in 2009.

4.3.2 Case ascertainment

Patients between 18 and 64 years old with a first episode of psychosis (psychotic coding F10–F29 and F30–F33 in ICD-10) were identified among those presenting for the first time to the three CMHCs within tightly defined catchment areas in West –Bologna, Italy over an 8 year period (January 2002- December 2009). The inclusion criteria are based on those used in the WHO study (Jablensky et al, 1992): i.e., presence of hallucinations, delusions, thought disorder, bizarre or disturbed behaviour, negative symptoms, mania, or clinical suspicion of psychosis; absence of an organic cause or profound learning disability; and no previous contact with psychiatric services for psychotic symptoms. A team of researchers was involved in checking weekly all patient contacts with the 3 CMHCs (Nani, Scalo and Tiarini) in the Bologna West Catchment Area. In Italy, CMHCs are services devoted to treating severe mental disorders and in Bologna Mental Health Department (MHD) almost all the patients with FEP are referred to CMHCs. Patients can be referred by many different agencies and self-referred (as described in Table 1). There were regular training events for staff. Each patient meeting inclusion criteria for the study was approached and informed consent sought.

Based on the methods used by Cooper et al. (1987), we conducted a leakage study after the survey period to identify any subjects missed by checking the list of patients recorded at the Bologna MHD in the study areas and reviewed all new mental health service registration forms held in the Bologna MHD, and interrogated computerized information systems.

Case notes were used to complete the Item Group Checklist (IGC), part of the SCAN (Schedule for Clinical Assessment of Neuropsychiatry, Version 2.1, World Health Organization-Division of Mental Health, Geneva 1998), to collect symptom-related data at the time of presentation and one month later to ensure that cases met ICD-10 criteria for psychotic disorders. Diagnoses were allocated by consensus agreement from a panel of psychiatrists at each study centre, including the principal investigator (IT) and the clinical researcher who completed the ICG-SCAN. For the analyses, we considered 5 diagnostic groups: 1) all psychoses, 2) affective psychoses (ICD F30-F33), 3) non-affective psychoses (ICD10 F20-29), 4) schizophrenia (ICD10 F20, including schizoaffective disorder F25), and 5) substance-induced psychoses (SIPs) (ICD10 F10-F19).

We coded ethnicity along with place of birth of the patient and his/her parents. We created a dichotomous ethnicity variable (Migrants (MI) vs Natives (NA), using the Municipality Registry. This classification includes the white non-Italian (predominantly East European) group in the MI category. In assigning patients to ethnic groups and in collecting other socio-demographic (age, marital status, education, housing, occupational status) and migration history information (birth origin, reason for migration, length of stay in Italy) we used a form developed specifically for the study (Bologna Migration History and Social Integration Interview). Age of onset was collected by asking the patients and/or key informants about when s/he experienced the first psychotic symptoms as defined above. Date of first contact with services was defined as the date when he/she was referred for the first time to Bologna West CMHC for his/her first episode of psychosis.

4.3.3 Statistical analysis

The variables examined included gender, age, age at FEP onset, marital status, place of birth, education, housing, occupational status, psychiatric diagnosis, pathways to care and

substance abuse. In order to identify the potential confounding effect of demographic and clinical variables in the relationship between MI, substance abuse and DUP, we used the chi-square, Fisher's Exact Test or Wilcoxon signed rank test. A multivariable logistic regression model was used to analyse the relationship between MI, marital status, pathways to care and duration of untreated psychosis (DUP), after adjusting for all the significant effects identified in univariable analyses. Median IR with interquartile range (IQR) and incidence rate ratios (IRR) with 95% confidence interval (CI) were calculated. Rates are presented per 100,000 inhabitants at risk per year. Data were analysed by SAS 9.1.3 for Windows.

4.4 Results

At mid-period the denominator population aged 18-64 in the catchment area was 116,013 (male n=57.804, 49.8 %; MI n = 1,.227, 9.7%) (see Table 1). Africans constituted 22.9% of the MI population, Europeans 32.7%, Asians 38.2%, Americans 6.1% and others (i.e., Oceania and persons without citizenship) 0.1%.

Two hundred and six people passed the initial screen and 14 were identified by the leakage study. We excluded 57 on the basis of further information: likelihood of ICD-10 organic psychotic disorder (n=7); probable non-psychotic disorder (n=2); FEP prior to the study period (n=44); no information or notes (n=1); outside study area (n=1); without residence permit (n=1); and older than 65 years (n=1). A total of 163 cases from the 3 CMHC met the inclusion criteria during the study period.

The majority of patients were men (*n*=92, 56%), and the mean age at onset was 30.5 ±9.32 and at first contact was 31.1±9.41. Most were single and living with their parental family; more than half had a high school certificate or more, and 59% had a job or were students. MI comprised 24% of the sample (Table 1).

4.4.1 Pathways to care and duration of untreated psychosis (DUP)

Access to CMHCs after psychiatric hospitalisation was the most frequent pathway to care and accounted for one third of referrals. The second most important source of referral was primary care, followed by informal pathways (self-referral, family or friends) and other health services (Table 4.1).

The large majority of the sample (84%) had a DUP shorter than 1 year. In a logistic regression model, after adjusting for gender and age at first contact, living alone and primary care referral (yes/no) were respectively associated with a 5-fold and 3-fold increased odd of a DUP longer than 1 year (Table 4.3).

4.4.2 Diagnoses

The large majority of patients received a diagnosis of non-affective psychosis (n=120, 74%), of whom 48% (n=77) received a diagnosis of schizophrenia, 16% (n=26) of brief psychotic disorder and 10% (n=17) of other non-affective psychosis. Affective psychoses accounted for 12% (n=20), of whom 7% (n=12) bipolar disorder, 5% (n=8) depression with psychotic features). Lastly, SIPs accounted for 14% (n=23). Moreover, 27 patients (16%) received a dual diagnosis (substance-related psychosis + other psychosis). (Table 4.1).

Table 4. 1. Denominator Population and Sample characteristics of the FEP Bo West

Mid-period denominator[a]	
Total	116 013 (100)
Sex	
Male	57 804 (49.8)
Female	58 209 (50.2)
Birth origin	
Native (NA)	104 786 (90.3)
Migrant (MI)	11 227 (9.7)
Cases	
Total	163 (100)
Male	92 (56.4)
Mean age (years)	31.1 ± 9.41
Mean age at onset (years)	30.5 ± 9.32
Marital status	
Single	117 (71.8)
Married	32 (16.6)
Separated	14 (8.6)
Birth origin	
NA	124 (76.1)
Emilia Romagna	73 (44.8)
Other Italian regions	51 (31.3)
MI	39 (23.9)
Education[b]	
Illiterate	1 (0.6)
Primary school/Junior high school	59 (38.1)
High school	71(45.8)
University degree and above	24 (15.5)
Housing[c]	
Alone	16 (9.9)
Parents	88 (54.3)
Partner/spouse	31 (19.1)
Other cohabitation	22 (13.6)
Social community	5 (3.1)
Occupational status[c]	
Workers	69 (42.6)
Unemployed	50 (30.8)
Students	27 (16.7)
Economically inactive	16 (9.9)
Pathways to care[c]	
Primary care referrals	43 (26.5)
Informal route	41 (25.3)
Psychiatric hospitalization	58 (35.8)
Other health services referrals	20 (12.6)
DUP[c]	
< 1 year	130 (83.9)
⩾ 1 year	25 (16.1)

FEP, First-episode psychosis; DUP, duration of untreated psychosis.

Values given as *n* (%) or mean ± standard deviation.

[a] Values refer to year 2005.

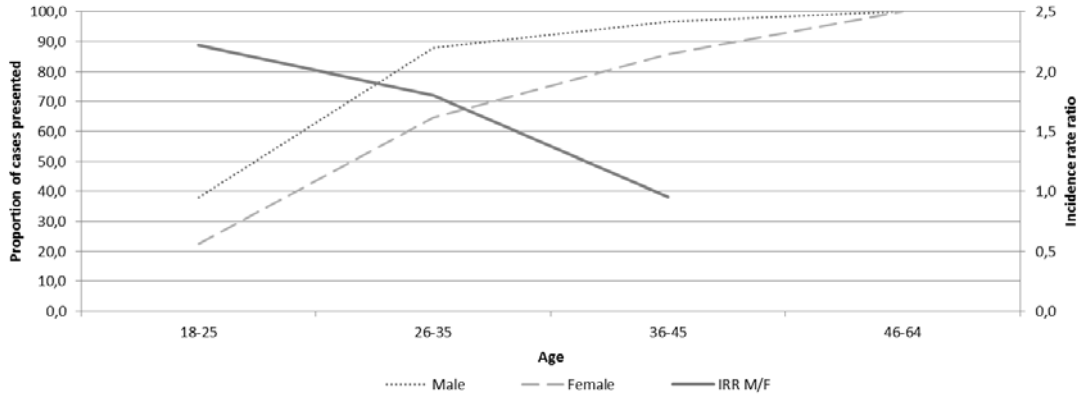
[b] Eight missing.

[c] One missing.

4.4.3 Age at onset and at first contact

More than 80% of men and 60% of women in the sample had a first contact with mental health services before 36 years of age (Figure 4. 5). For all psychoses, the mean age at first contact was significantly younger for men (28.9 years [95% CI, 27.2-30.5]; median age 28 [inter quartile range 24-33]) than for women (33.8 years [95% CI, 31.4-36.2]; median age 34 [inter quartile range 31- 36]). As with the age at first contact, the mean age at onset for all psychoses was significantly younger for men (28.6 years [95% CI, 26.9-30.3 years]; median 28 years [inter quartile range 23-33]) than women (32.9 years [95% CI, 30.5-35.3]; median 30 years [inter quartile range 26-38]). Similar patterns were observed separately for non-affective psychosis, but not for affective or substance-related psychosis. For these diagnostic groups we did not find any age differences at first contact between men and women.

Figure 4.5 Cumulative proportion of all psychoses by sex and age and IRR's for males compared with females



4.4.4 Median annual incidence rates

The overall median IR for all psychotic disorders was 16.4 per 100,000 inhabitants per year (IQR 14.3-17.8). The median IR for non-affective and affective psychoses was respectively 11.3 per 100,000 per year and 1.7 per 100,000 per year. The median IR for SIPs was 2.6 per 100,000 per year and that for schizophrenia was 7.3 per 100,000 per year.

The incidence of psychosis was significantly increased in younger age groups compared with the reference category (age 46-64). In particular, it was 25 times higher among those

aged 18-25, 15 times higher among those aged 30-35 and 2 times higher among those aged 36-45. Similar IRRs were found when considering age at first contact. These associations were specific to non-affective psychoses (and schizophrenia) and to SIPs ; no association was observed between age and affective psychoses (Table 4.2).

IRRs for all psychoses, for schizophrenia and for SIPs were higher for men than women. Sixty-five percent of patients with schizophrenia and 70% of those with SIPs were men. Other non-affective psychoses and affective psychoses were more frequent among women (58% and 60% respectively). The incidence for men was higher than for women at younger ages, but as age increased, the difference disappeared. As shown in Figure 1, the highest IRRs for all psychoses for men vs. women occurred in the 18 to 25 years age group (IRR, 2.2 [95% CI, 1.6- 2.8]). The IRR decreased beyond age 25 years and at 35-45 years it was close to 1. A similar pattern was observed for non-affective psychoses.

All MI were first-generation. For all psychoses, the IRR for the MI population was 2.530 (95% CI, 2.170-2.890). Compared with NA, in MI the incidence was higher for non-affective psychoses (IRR 3.4, 95% CI 3.0 - 3.8) and in particular for schizophrenia (IRR 4.1, 95% CI 3.6 - 4.5).

Table 4. 2. Median Annual Incidence rate of various Psychoses x 100.000

	Psychoses		Non-affective psychoses (F20–F29)		Affective psychoses (F30–F33)		Substance-related psychoses (F10–F19)		Schizophrenia (F20 and F 25)	
	Rate (IQR)	IRR (95% CI)	Rate (IQR)	IRR (95% CI)	Rate (IQR)	IRR (95% CI)	Rate (IQR)	IRR (95% CI)	Rate (IQR)	IRR (95% CI)
Age at onset (years)										
18–25	54.6 (50.6–64.5)	**25.394 (24.787–26.001)**	34.3 (27.6–38.4)	**15.998 (15.296–16.701)**	0.0 (0.0–8.6)	–	13.6 (9.1–26.4)	**3.765 (2.928–4.602)**	22.4 (15.7–29.3)	**6.709 (5.976–7.443)**
26–35	32.4 (29.9–37)	**15.074 (14.485–15.663)**	25.1 (20.4–34.6)	**11.7 (11.029–12.37)**	1.9 (0.0–6.8)	1.155 (0.008–2.303)	3.6 (0.0–6.8)	Ref.	16.3 (14.2–18.6)	**4.874 (4.178–5.571)**
36–45	5.0 (3.3–7.5)	**2.332 (1.640–3.023)**	3.3 (3.2–4.4)	1.557 (0.767–2.347)	1.6 (0.0–3.3)	Ref.	0.0 (0.0–0.0)	–	3.3 (0.0–4.4)	Ref.
46–64	2.1 (1.6–4.3)	Ref.	2.1 (1.6–2.7)	Ref.	0.0 (0.0–0.5)	–	0.0 (0.0–0.0)	–	0.0 (0.0–2.1)	–
Age at first contact (years)										
18–25	53.5 (49.4–71.1)	**24.882 (24.273–25.491)**	35.3 (24.7–43.1)	**16.475 (15.767–17.182)**	0.0 (0.0–8.5)	–	13.6 (9.1–26.4)	**3.765 (2.928–4.602)**	22.0 (9.2–31.4)	**6.601 (5.859–7.344)**
26–35	34.1 (27.5–37.2)	**15.887 (15.299–16.475)**	28.7 (20.4–33.5)	**13.378 (12.709–14.048)**	3.6 (0.0–4.5)	1.110 (0.020–2.201)	3.6 (0.0–6.8)	Ref.	18.0 (14.2–22.3)	**5.397 (4.705–6.090)**
36–45	6.5 (3.5–7.5)	**3.009 (2.329–3.689)**	3.3 (3.2–4.4)	1.557 (0.776–2.338)	3.2 (0.0–3.3)	Ref.	0.0 (0.0–0.0)	–	3.3 (0.0–4.4)	Ref.
46–64	2.1 (1.6–4.3)	Ref.	2.1 (1.6–2.7)	Ref.	0.0 (0.0–0.5)	–	0.0 (0.0–0.0)	–	0.0 (0.0–2.1)	–
Gender										
Male	19.1 (15.1–24.5)	**1.394 (1.085–1.704)**	11.3 (9.9–20.2)	1.202 (0.841–1.563)	1.7 (1.3–2.2)	1.000 (0.105–1.895)	3.5 (3–5.2)	**3.889 (2.957–4.821)**	11.2 (4.8–14)	**2.154 (1.686–2.622)**
Female	13.7 (11.1–16.9)	Ref.	9.4 (6.9–13)	Ref.	1.7 (0.0–3.9)	Ref.	0.9 (0.0–3.4)	Ref.	5.2 (4.7–7.3)	Ref.
Ethicity										
Migrant	38.8 (31–48.7)	**2.530 (2.170–2.890)**	33.9 (25.5–41.8)	**3.389 (2.985–3.794)**	0.0 (0.0–1.6)	–	0.0 (0.0–8.6)	–	26.3 (18.3–28.5)	**4.046 (3.558–4.534)**
Native	15.3 (12.8–15.9)	Ref.	10.0 (8.6–12.8)	Ref.	1.4 (1.0–2.8)	Ref.	2.4 (1.7–3.2)	Ref.	6.5 (3.9–8.1)	Ref.
Total	16.4 (14.3–17.8)		11.3 (10.1–14.2)		1.7 (0.9–3.0)		2.6 (1.7–3.4)		7.3 (6.5–10.7)	

IQR, Interquartile range; IRR, incidence rate ratio; CI, confidence interval.
Statistically significant results appear in bold.

4.4.5 Ethnicity

We found several significant differences between the MI group and NA. Using logistic regression and controlling for age and gender, patients in the MI group were significantly more likely to be working, married and live outside the family of origin. MI are more frequently referred to our CMHC after psychiatric hospitalization or by GPs. (Table 4. 3). There was no age difference between male and female MI at the time of psychotic onset and at first contact.

Table 4.3 Predictors of DUP, migrants' status and substance abuse. Results from logistic regression models [a]

	DUP (>1 *v.* ⩽1)		Migrants (Yes *v.* No)		Substance abusers (Yes *v.* No)	
Predictor	aOR (95% CI)	*p* value	aOR (95% CI)	*p* value	aOR (95% CI)	*p* value
Gender						
Male *v.* Female	0.842 (0.296–2.391)	0.746	1.121 (0.458–2.744)	0.803	**3.272 (1.301–8.213)**	**0.012**
Age	1.027 (0.966–1.093)	0.391	0.965 (0.915–1.019)	0.201	**0.811 (0.737–0.892)**	**<0.001**
Live alone						
Yes *v.* No	**14.831 (2.140–102.529)**	**0.006**	0.309 (0.062–1.552)	0.154	1.050 (0.200–5.506)	0.954
Worker						
Yes *v.* No	**0.313 (0.102–0.959)**	**0.042**	**3.761 (1.540–9.188)**	**0.004**	**3.499 (1.213–10.092)**	**0.021**
Married						
Yes *v.* No	1.758 (0.252–12.281)	0.569	2.143 (0.610–7.525)	0.234	–	–
Live outside the family of origin						
Yes *v.* No	0.325 (0.060–1.771)	0.194	**4.035 (1.405–13.189)**	**0.011**	1.156 (0.430–3.110)	0.774
Native						
Yes *v.* No	0.670 (0.173–2.587)	0.561	–	–	**4.716 (1.381–16.107)**	**0.013**
Primary care referral						
Yes *v.* No	**3.154 (1.016–9.796)**	**0.047**	**3.180 (1.030–9.819)**	**0.044**	0.562 (0.190–1.667)	0.299
Psychiatric hospitalization						
Yes *v.* No	0.310 (0.071–1.361)	0.121	**3.765 (1.297–10.932)**	**0.015**	1.550 (0.605–3.973)	0.361

DUP, Duration of untreated psychosis; aOR, adjusted odd ratio; CI, confidence interval.
[a] Adjusted for all the variables in the table.

4.4.6 The BoFEP substance abusers

About one in three of the sample were current substance abusers. All FEP abusers are younger than 35 years old. Table 4.4 describes the distribution of substances used in the sample: cannabis was the most common, with ¾ of multi-abusers smoking cannabis. Among users, 23 received a simple diagnosis of SIPs (F10-19); 27 received a dual diagnosis of non-affective psychosis (F20-29, n=22) or affective psychosis (F30-33,n=5) and substance-related disorder (abuse or dependence). Abusers were significantly younger at

the onset of psychosis (24.8 ± 4.7 vs. 33.0 ± 9.8, p<0.0001) and at first contact with psychiatric services (25.3 ± 4.6 vs. 33.6 ±9.9, p<0.0001).

FEP substance abusers were more frequently male. After adjusting for age and gender, patients with substance abuse were 2.8 times more likely to be native (Table 4.3).

The previously observed difference between female and male in age at first contact with a CMHC disappeared when only FEP abusers were included in the analysis (male 25.7 years ± 4.8, female 22.7 ±3.9, p=0.1391).

Table 4.4. Substance abuse

All substance abusers	50 (30.7)
Single abuser	22 (45.8)
Polyabuser	26 (54.2)
Substance[a]	
Alcohol	22 (44.0)
Only alcohol	2 (4.0)
Cannabis	37 (74.0)
Only cannabis	18 (36.0)
Stimulants/hallucinogens	16 (32.0)
Only stimulants/hallucinogens	1 (2.0)
Opioids	6 (12.0)
Only opioids	1 (2.0)

Values given as *n* (%).
[a] Two missing.

4.5 Discussion

4.5.1 Principal findings

This is the first incidence study carried out in Italy on prospectively identified and evaluated individuals with a FEP. We found an overall incidence rate of psychosis of 16.4 per 100,000. Other psychosis-incidence studies already available in Italy are based on case-registers or data concerning admission to general psychiatric hospitals (Thornicroft et al., 1993; Preti et al., 2000). Interestingly, our finding of an overall schizophrenia IR of 7.3 per 100,000 is very similar to the mean rate of first admission to general hospital psychiatric services for schizophrenia found by Preti et al (2000). We also found an increased incidence of psychosis in young people, men and MI, after adjusting for gender and age. In particular,

the incidence of psychosis was more than three times the overall rate in those aged 18-25 years (54.6 per 100,000).

4.5.2 Comparison with other FEP studies

Overall the IR of FEP we found is lower than the IR previously found by other studies carried out in UK (Kirkbride et al, 2006; Coid et al., 2008; Cheng et al, 2011) and in other north Europe countries (Cantor-Grae et al., 2005; Lao et al 2006; Veling et al., 2006). Even if we did not perform a directly statistical comparison between the results of our study and previously studies, the incidence we found seems to be quite near the incidence found in Bristol (Kirkbride et al., 2006) and in South Cambridgeshire (Cheng et al., 2011), both overall and for the youngest groups (18-36 years old) particularly for schizophrenia.. Overall Bologna is less deprivated, ethnically heterogeneous than many European areas where other studies have been conducted. For instance, Bologna is an urban area with a high degree of social cohesion and low population mobility. The distribution of putative social risk factors for psychosis varies with the different population-groups. Although the Bologna population is among the oldest in the world, with one in four citizens older than 65, migrants and students are two younger groups characterized by much greater economic instability and lower social cohesion than is found among Bologna's other inhabitants (Provincia di Bologna, 2007). Thus the low overall rates mask higher rates in these groups. Bologna is a recent focus of immigration and most of the migrants living in this area are first-generation young migrants at the beginning of their adaptation process to the host society. Interestingly, we found an IR similar to the IR found in Brazil, Sao Paolo (Menezes, et al., 2007). The incidence found in the Sao Paolo study was actually lower than expected in such a vast urban place. In this regard, Kirkbride & Scoriels (2009) stated that socio-environmental processes involved in the aetiology of schizophrenia seems to be more complex than simple linear associations with urbanicity. Social organisation, for example the prevalence of people living with families and level of social cohesion, should evaluated by further studies to try to explain similarities in psychosis rates among those studies,

However, within the context of an overall lower incidence of psychoses, we found the same socio-demographic correlates of incidence, such as age, gender and ethnicity, as found in northern European studies. We confirmed the age-at-first-contact pattern previously observed for schizophrenia (Hafner et al., 1993; Kirkbride et al., 2006): we show the classic

excess for men at younger ages, followed by a later decline, with a non-significant rise in the incidence of psychoses for women older than 40. We found a greater incidence of schizophrenia and SIP for men than for women, as found by previous studies (Aleman et al, 2003; Kirkbride et al., 2006). Like Kirkbride et al. (2006), we confirmed that the commonest time of onset for affective psychosis is in early adulthood, as in schizophrenia, but the pattern for men and women is much more similar. The higher risk for FEP we found among MI is consistent with the mean weighted incidence rate ratios (2.3, 95% CI 2.0-2.7) found in the recent meta-analysis of Bourque et al (2001).

4.5.3 Pathway to care and duration of Untreated Psychosis (DUP)

We found some socio-demographic factors associated with a DUP of one-year or more: particularly, living alone and being referred by a PC. Living along has been already demonstrated in Italy to be associated with difficult psychiatric services utilization (Thornicroft et al., 1993). Last result could be seen as paradoxical since, for those with severe mental disorders, the most appropriate pathway to care is from GPs to CMHCs. However, in Italy CMHCs can also be directly accessible, without GPs referrals. It is possible that, to live alone and to be referred by a GP could be proxy variables for higher functioning and a lower severity of psychopathology, that could lead, in several cases, to a delay of specialized-psychiatric treatment and referrals to CMHCs. At the other end, patients living with others and with a good social network may directly access the CMHC with a shorter DUP. As shown in previous studies, the absence of family involvement in seeking help is related to a longer DUP (Morgan et al, 2006).

4.5.4 Migrants (MI)

We observed a 2.5 times increased incidence of psychoses in the MI group compared with the NA group, consistent with the result of the meta-analyses of Bourque et al. (2011). In our BoFEP sample, FEP MI seem to have a higher level of social functioning: a higher proportion are workers and live outside the parental family, in contrast to natives. These findings could indicate that socio-environmental risk factors not included here (such as individual social class and social capital; psychological effects such as life events, achievements, and expectations; and neighbourhood deprivation) (Broome et al, 2005; Morgan et al., 2007b) could be relevant. It is also possible that different exposure to

biological factors (such as unknown environmental contaminants, diet, infectious agents, etc) (Mc Grath et al, 2004b; Brown et al., 2004) may be etiologically relevant in explaining the differences in incidence rates we observed between MI and NA, following the socio-developmental model of Morgan et al (2010). Further studies, with population based control groups for comparison, such as the recently started pan-European EUGEI European Network of National Schizophrenia Networks Studying Gene Environment Interactions) will allow a deeper understanding of the nature of the socio-demographic differences found among FEP NA and FEP MI (van Os et al., 2008).

In line with the AESOP Study (Morgan et al., 2006), we did not find any evidence that the DUP was longer for MI patients than for NA patients. In the UK, research has consistently shown that black Caribbeans are not only at greater risk of developing psychosis, but are also more likely to access mental health care via adversarial routes, often involving the police and compulsory admission, and more likely to be treated in secure and forensic settings (Morgan et al, 2006). Our study showed evidence for a more frequent pathways to CMHC care after psychiatric hospital admission and after GPs referrals: direct access to Bologna west CMHC is less frequent among MI compared to NA. This could be due to different factors, related to MI patients and also to our psychiatric services, such as different attitudes towards mental health services among MI, and residual low cultural attractiveness of psychiatric services. The authors of the AESOP study (Morgan et al., 2006) conjecture that there are ethnic differences at first contact, and consequently that processes within these communities might increase the risk of an adverse pathway to care prior to contact with services. This hypothesis needs further clarification in future studies.

4.5.5 Substance abuse

Our findings also show that substance use, particularly cannabis use, is associated with FEP: around one in three of our BoFEP cases are currently substance abusers, a markedly higher proportion than among young people in the general population (8%; Diaprtimento Politiche Antidroga, 2010). At onset substance abusers are significantly younger compared to not abusers. We know early onset is associated with worst outcomes (McGorry et al., 2011). Further longitudinal studies are needed to better clarify the casual relationship between cannabis use and psychosis onset and course. However, the evidence of an earlier psychosis onset in cannabis abusers could be considered as further evidence for the causal

relationship between cannabis use and psychosis onset, as Large et al. concluded in their recent meta-analysis (2011).

4.6 Methodological considerations and limitations

To our knowledge, this study is one of the first investigations of prospectively ascertained and clinically assessed FEP of psychosis in Italy. This is a CMHC-based incidence study capturing all potential cases who made contact with mental health services within the catchment area and leakage studies were conducted to minimize under-ascertainment.

Some cases completely covered by the private sector (probably milder cases) may not have been included in the study. In Bologna, the public service is widespread across the territory and involves partnerships with private psychiatry. We must also remember that, as stipulated by the organization of Italian CMHCs, patients with psychosis are not seen solely by the GP, but always in collaboration with a CMHC psychiatrist. We know that usually FEP patients are not treated at only primary care level, however we might have missed some cases, particularly those with less severe psychopathology and a higher socio-economic position who tried to avoid the public health services and seek care in the private sector. Although a great effort was made to identify all potential cases of FEP, we could not rule out some possible underestimation of FEP incidence in the Bologna West catchment area. However, cases that did not access CMHC directly or by GPs or other services referrals could be underestimated, because we only performed a post-hoc linkage study based on data available in Bologna MHD.

Consensus diagnoses were performed blind to the ethnic status of the case. Acknowledging that the true dynamic population at risk over the survey period may have varied slightly, denominators for the population at risk of psychosis were derived for each year from the Municipality Registry. Thus, we have no reason to believe that there was any systematic bias or under-enumeration of minority ethnic groups, male, and younger people. We minimized any misclassification of ethnic status in either our denominator or our numerator populations by using a dichotomous ethnicity variable with a very broad MI group and an easily definable comparator group.

4.7 Conclusions

In our study we found that the incidence of schizophrenia and other psychotic syndromes varies according to age, gender and ethnic group. Thus, we think that this study adds a contribution to our understating of the role of the major environmental candidates in FEP, such as gender, age, ethnicity, substance use and social organisation which seem to be pathogenetic in Italy as well as in Northern Europe. These findings have implications for policy and mental health service development, since it seems possible to develop targeted prevention intervention for risk groups, such as youth, MI and substance abusers.

We found the overall incidence rate standardised for age and gender in the BoFEP study was 16.4 per 100,000 person-years (95% CI, 13.9-18.9). The incidence was higher in young people, men and migrants. The incidence of FEP found by the Bologna study is lower than incidence found in northern European studies. However, as in other studies, the incidence was higher in migrants. For all psychoses, the IRR for the MI population was 2.530 (95% CI, 2.170-2.890). This result is very similar to the IRRs found by other studies conducted in different European countries (Table 4.5).

Table 4.5 Comparison of IRR of psychosis in first generation migrants in EU

Host Country	**IRR**	**95% CI**
Italy (Bologna)	2.5	2.2-2.9
The Netherlands*	2.5	2.0–3.2
Scandinavia*	2.3	1.9- 2.7
UK*	2.8	2.2-3.5

*From Bourque et al, 2011

Chapter 5: Study 2- Risk of psychosis in internal migrants in Italy: results from the Bologna First Episode Psychosis Study

5.1 Background of the study 2

So far as we know no studies have been conducted after the pioneer Odegard's study that consider not only external migrants but also internal migrants. Thus very little is known about the relationship between First Episode Psychosis (FEP) and internal migration within a country. Demonstrating a relationship between internal migration and psychosis incidence could add evidence as to the role of migration itself (versus ethnicity) in increasing the risk of psychosis.

This study aimed to evaluate: incidence rates in natives (NA born in Emilia Romagna), Internal migrants (IM born in other regions), external migrants (EM born outside Italy); risk factors for FEP in an attempt to explain differences in incidence rates.

Before introducing the study 2 , I briefly describe the internal migration phenomenon in Italy.

5.1.1 Internal migration in Italy and in Bologna

After World War II, Italy became in a few years an industrial country. This provoked a major migratory movement which took effect as a giant mixing of the population in the country. The advent of 'industrialization in fact demanded strong contingent of workers from other countries, and especially from the countryside and consequently the population density of the city showed a very strong growth. The rural population, generally devoted to agriculture, began to migrate in large industrial centers in North-Western: Turin, Milan, Genoa (Fofi, 1976; Paci, 1976; Ramella, 2003, Badino, 2008). Even large cities of the South, and especially Rome were the destination of important migratory flows (Ascoli, 1979; Ginsborg, 1998). It was mainly during the sixties that a massive migration brought many workers from rural areas of the South to the industrialized regions and cities of northern Italy that could provide jobs in their factories. Typical is the case of Turin, where the industry FIAT absorbed large numbers of workers, to the point that in some areas more than 80% of the workers was of southern origin. In the 80's migration to the large urban centers decreased, while the

city of small and medium size began to increase (Gesano, Golini, 1993). In the 90's South-North migration again becomes conspicuous, and while not returning to be as important as in the past, it is still of major importance (Pugliese, 2006). From 1946 to now about six million Italians emigrated abroad, while in the same year more than 17 million Italians changed residence, moving for work across the country, but especially in the industrial cities of central and northern.

Analyzing the regional migration balance (total incoming people - total people in output), a recent analysis of Istat (2013) highlights a pronounced dualism between the Centre- South, which reported major losses in particular in Campania, Puglia and Sicily and the North of the country which registers a positive balance. In particular, the Emilia Romagna is, after Lombardy, the second Italian region for positive migration balance. In Emilia Romagna, one of the main site of internal immigration is the capital Bologna, which is in seventh place among the Italian most populated cities, with 384 202 inhabitants and a population density of 2730.6 / sq km (square kilometer).

5.2 Introduction

Recent theories consider the increased risk of psychosis in migrants as the result of a complex interaction between biological vulnerability and environmental factors throughout the migration process. Morgan (Morgan et al., 2010 introduced the social development model of psychosis, where environmental factors can act both individually and socially. Bourque (Bourque et al., 2011) showed in the UK that black minorities have the highest risk, while in the Netherlands recent North African immigrants with a lighter skin color had the highest risk. It is therefore very important to understand which are the specific characteristics of each host society that interact with migration characteristics to increase the risk of psychosis. It seems necessary to look for the risk of psychosis in the "immigrant status" rather than in "immigrant": "immigrant status" means the special meeting between the migrant and the host country. Perhaps the nature of this meeting could explain the increased risk of psychosis in migrants in different countries.

From this prospective, it could be very interesting to study also the incidence rate of psychosis in people who migrated within the country where they are born. Unfortunately, very little is known about the relationship between psychotic disorders and internal

migration, because almost all studies only investigated the phenomenon of external migration. The only research conducted on the subject are those of Malzberg, published in 1962 (Malzberg, 1962), with regard to migrants from other U.S. states residing in the state of New York, and of Odegard and Asturp published in 1960 (Asturp & Odegard, 1962) on internal migration in Norway. Malzberg compared the raw and adjusted for age and sex, incidence rates of schizophrenia and other psychotic disorders, among the native population of New York and the migrants from other U.S. states, finding a higher incidence in internal migrants than natives. The work of Odegard however, conducted on internal migration in Norway, showed that the incidence rates of psychotic onset disorders were significantly lower in the internal migrant population than natives. Particularly low incidence rates were observed in the migrants who came from short distances (within the same county) and migrants who moved from rural areas into urban areas. Migrants who moved instead from urban areas to rural areas had higher incidence rates. A possible explanation given for these last data was the fact that this type of migration was more atypical for the population. The striking exception was the city of Oslo, in which the population of internal migrants had higher incidence rates than natives, this particularly evident in females.

No modern study has been conducted to explore the relationship between psychosis and internal migration and to compare between them different types of migratory route, in an attempt to explain the difference in the risk of developing psychosis. The aim of this study is therefore to describe the relationship between psychosis onset and migratory phenomenon in all of its dimensions, by dividing the population into three groups: Native in Emilia Romagna (Northen Italy), Internal migrants (from other Italian regions, mainly Southern Italy) and External migrants (from other countries). The incidence rates observed will be compared to test whether there is a gradient of incidence between the three groups under consideration, that is, if the incidence rates are increasing or not as the migration distance increases. In addition, for each of the groups considered, the prevalence of established risk factors for psychotic onset will be described and compared (Tarricone et al. 2012). These are gender, age at first contact, marital status, education, housing, occupational status, substance use, in a preliminary attempt to explain what risk factors might underlie the differences in risk of psychotic disorders across the three groups of patients. We also

evaluated possible difference of pathways to care and DUP among the 3 groups of patients (Natives, internal migrants and exterenal migrants).

5.3 Setting and methodology

This study is part of the FEP-Bo project (First Episode Psychosis Bologna), which studies the incidence of psychotic disorders and assesses all new cases at presentation. In particular, this study includes all new cases of psychosis identified between January 2002 and December 2010 at three Community Mental Health Centers (CMHCs Nani, Scalo and Tiarini) that cover the resident population of the West Bologna. The districts that refer to these CMHCs are Borgo Panigale, Navile, Porto, Reno and Saragozza. The area of west Bologna is an exclusively urban area with a high degree of social cohesion and low ethnic heterogeneity.

5.3.1 Population at risk

The Bologna west catchment area includes around half of the total population of Bologna. The data concerning the population at risk were obtained from the ISTAT Census of 2001 and further supplemented by the Statistics Sector of the Municipality of Bologna and the registry office of the AUSL, for each year of the study. The population used as denominator includes all the residents between 18 and 64 years of age (mid period population, 2006 year: 114,993 inhabitants: 67,887 (59.1%) natives, 31,448 (27.4%) internal migrants (of whom 25,247, 80%, from South Italy) and 15,568 (13.5%) external migrants.

5.3.2 Inclusion criteria of the cases

This study included all the cases, between 18 and 64 years, with a first episode of psychosis (encoding F10-F29 and F30-F33 in ICD-10) who made contact for the first time with one of three CMHCs living within the pre-defined catchment area in the west Bologna, for a period of 9 years (January 2002-December 2010). These three CMHCs have had special FEP programs in place for several years, including a particular program of consultation and connection with the general practitioners (GPs) and other agencies, developed in the late 1990s, to facilitate better identification of new cases of first psychotic episodes (Berardi et al. 1999).

The symptom and sign inclusion criteria used are based on those used in the World Health Organization (WHO) study (Jablensky et al. 1992): that is the presence of hallucinations, delusions, thought disorder, bizarre or disturbed behavior, negative symptoms, mania or clinical suspicion of psychosis; absence of an organic cause or profound learning disability; and no previous contact with psychiatric services for psychotic symptoms. A team of researchers has been involved in the weekly monitoring of all patient contacts with the three CMHCs (Nani, Scalo and Tiarini) in the west Bologna catchment area. There has been periodic training for the health professionals. Each patient who met the inclusion criteria for the study was contacted and gave their informed consent. After the investigation period, based on the methods used by Cooper et al. (1987), we conducted a leakage study to identify any missed case by checking the list of patients recorded at the Bologna Mental Health Department MHD) in the study areas. We reviewed all mental health service registration forms held in the Bologna MHD and checked the computerized information systems. Case-notes were used to complete the Item Group Checklist (IGC), part of the Schedule for Clinical Assessment of Neuropsychiatry, Version 2.1 (SCAN; WHO, 1998), to collect symptom-related data at the time of presentation and 1 month later to ensure that cases met ICD-10 criteria for psychotic disorders.

5.3.3 Statistical analysis

Both the population at risk and the cases of FEP were stratified by gender, age groups of ten years and ethnicity. With regard to ethnicity there were three distinct groups: the natives, that is, people born in Emilia Romagna (Northern Italy); the internal migrants, that is, people born in other regions of Italy (mostly Southern Italy) and migrated in Emilia Romagna; the external migrants, that is, people born abroad and immigrated in Italy.

We calculated the crude incidence rates for all groups of patients examined: by gender, by age and by migration status. Directly standardized incidence rates, standardized for age and gender were calculated using the distdze command in Stata 10, with the standard considered as the entire study population. The incidence rates are presented per 100 000 person years. There was overdispersal in the distribution of the cases with the variance considerably greater than the mean. Negative binomial regression was therefore carried out to estimate the effect of migrant group after adjusting for age and gender.

The variables examined include gender, age at first contact, marital status, education, occupational status, pathway to care, housing, DUP, diagnosis and substance abuse. Population levels of risk factors stratified by age, gender and migrant group were not available. Therefore the prevalence of the risk factors, diagnoses and substance misuse were analyzed among the 3 groups were analyzed using one way-Anova test and chi square test to compare categorical and continuous variables. These analyses were done using SPSS for windows.

5.4 Results

A total of 187 cases met the inclusion criteria during the study period, of which: NA 82 (43.9%); IM 61 (32.6 5%); EM 44 (23.5 %). Among internal migrants, 42 (68.9%) came from South Italy. The majority of patients were men (n=108, 57.8%). This was also true for all the three groups of patients: NA, IM, EM, with no significant differences between them. The age at first contact was 31.3 years, with no significant difference between the three groups of patients.

5.4.1 Description of the sample (Table 5.1)

The majority of patients were single (136, 72.7%), but there was a significant difference among the three groups ($p<0.001$). The highest proportion of single people were in the IM group, followed by the NA. The highest proportion of married patients were in the EM group (15, 34.1%). The NA more often lived with their parents (57, 70.4%); the IM had the highest number of cases who lived on their own (17.9%); the EM more frequently lived with step family or friends (24, 54.5%). The difference in living status among the three groups of patients was found to be statistically significant ($p<0.001$).

More than half of the three groups of patients had a high school certificate or more. The differences between the three groups in education of patients were not statistically significant ($p=0.206$).

The majority of the cases were employees (41.9%) followed by the unemployed (32.3%). Unemployment was greater in IM and lower in EM. 57% of EM were employees and only around 1 in 3 of IM were employed. Students represented only 7% of EM, i.e. almost 3 times less than NA and IM.

All patients with first episode psychosis in Bologna are referred to the CMHC which has territorial jurisdiction for the area where the patient lives. Access to CMHC after psychiatric hospitalization was the most frequent pathway to care and accounted for one third of the referrals The second most important source of referral to CMHCs was primary care (27.0%) .This was also true for the immigrant populations. The EM however came into contact with CMHCs most frequently after a psychiatric hospitalization (43.3The EM were reported by family members less than the other two groups (5.7%): approx. one quarter of the NA and one third of the MI. Most of the cases in all three groups of patients had a DUP <1year (over 80%). Cannabis use at onset was present in 25.5% of cases. The IM were those who used more of this substance (34.4%). The EM used it half as much than the NA and IM.

Table 5. 1. Socio-demographic and clinical characteristics of the sample

	Natives (NA) n(%)	**Internal migrants (IM) n(%)**	**External migrants (EM) n(%)**	**Total N (%)**	**p**
Socio- demographic characteristics					
Mean age at first contact ± SD	31.2±10.2	31.5±10.5	31.0±7.7	31.3±9.7	P=0.97
men	49 (59.82)	33 (54.1)	26 (59.1)	108 (57.85)	P=0.778
Marital status					***P<0.019***
Single	61 (74.4)	51 (83.6)	24 (54.5)	*136*	
Married	12 (18.3)	6 (9.8)	15 (34.1)	*(72.7.4)*	
Separated	6 (7.3)	4 (6.6)	*5 (11.4)*	*36 (19.3)*	
				15 (8)	
Education (6 missing)					P=0.206
Illiterate	0 (-)	0 (-)	1 (2.4)	1 (0.6)	
Primary school/Junior high school	31 (39.2)	19 (31.1)	21 (51.2)	71 (39.2)	
High school					
University degree and above	37 (46.8)	31 (50.8)	13 (31.7)	81 (44.8)	
	11 (13.9)	11 (18.0)	6 (14.6)	28 (15.5)	
Occupational status (1 missing)					*P=0.117*
Unemployed	23 (28.4)	23 (37.7)	14 (31.8)	60(32.3)	
Workers (employed)	29 (35.8)	18 (29.5)	23 (52.3)	70(37.6)	
Own workers	3 (3.7)	3 (4.9)	2 (4.5)	8(4.3)	
Economically inactive	11 (13.6)	3 (4.9)	2 (4.5)	16(8.6)	
Students	15 (18.5)	14 (23.0)	3 (6.8)	32 (17.2)	
Housing					**P<0.001**
Alone	5 (6.2)	12(19.7)	4 (9.1)	21 (11.3)	
Parents	57 (70.4)	26 (42.6)	16 (36.4)	99 (53.2)	
Partner/Spouse	15 (18.5)	6 (9.8)	14 (31.8)	35 (18.8)	
Other	4 (5.0)	17 (27.9)	10 (22.7)	31 (16.7)	
Clinical Information					
Diagnoses					P=0.762
Affective psychoses	13 (15.9)	12 (19.7)	9 (20.5)	34 (18.2)	
Non affective psychoses	69 (84.1)	49 (80.3)	35 (79.5)	153 (81.8)	
Pathways to care					*0.102*
Primary care	18 (21.9)	14 (23.0)	18 (40.9)	50 (26.6)	
Informal route	27(32.9)	17 (27.9)	7 (15.9)	51 (27.1)	
Psychiatric hospedalization	26 (31.7)	21 (34.4)	18 (40.9)	65 (34.6)	
Other services referrals					
	11(13.4)	9 (14.8)	1 (2.3)	22 (11.7)	
DUP (35 missing)					P=0.693
<1year	58 (82.9%)	42 (87.5%)	30 (81.1%)	130	
>= 1 year	12 (17.1%)	6 (12.5%)	7 (18.9%)	(83.9%)	
				22 (16.1%)	
cannabis use (3 missing)	20 (25.0%)	21 (34.4%)	6 (14.0%)	47 (25.5%)	*P=0.061*
alcohol (2 missing)	10 (12.3%)	10 (16.4%)	3 (7.0%)	23 (12.4%)	P=0.358
Stimulants/hallucinogens (3 missing)	6 (7.5%)	6(9.8%)	2 (4.7%)	14 (7.6%)	P=0.617
Opioids (3 missing)	2 (2.5%)	3 (4.9%)	1 (2.3%)	6(3.3%)	P=0.671

5.4.2 Annual incidence rates and incidence rate ratios

Table 5.2 shows the crude incidence and standardised incidence for age and sex for all the three groups

Table 5. 2 Crude and directly standardized Incidence rates (cases per 100,000 population)

	Crude Incidence	Adjusted Incidence*	IC 95%
Natives NA	12.0	12.6	[9.7- 15.5]
Internal Migrants IM	21.3	25.3	[18.6, 31.9]
External Migrants EM	28.00	21.4	[14.6, 28.2]

*adjusted for age and sex

In table 5. 3 we report IRR, adjusted for age and sex, for both groups of migrants compared to the native population from the negative binomial regression model.

Table 5. 3. Incidence Rate Ratio for internal and external migrants compared to natives in Emilia Romagna Region

	IRR*	95% CI	p
Natives NA	Ref.	Ref.	Ref
Internal Migrants IM	1.93	[1.19 - 3.13]	0.007
External Migrants EM	1.79	[1.06- 3.02]	0.03

*adjusted for age and sex

5.5 Discussion

Our study shows that internal migrants, mostly from Southern Italy had higher incidence rates of psychosis, similarly to migrants from outside Italy, than native Italians born locally. The Italian migrants also had the highest prevalence of several known environmental risk factors for psychosis, such as unemployment, single status, living alone and cannabis use. The literature on the incidence of psychosis in internal migrants is sparse and somewhat dated. As described above a higher incidence rate in internal migrants compared with the

native population is confirmed by the study of Malzberg in 1962 in New York. According to the study of Odegard in 1960, this was also true for internal migrants to the city of Oslo. To extend the discussion of our results, given the lack of recent literature on the subject "internal migration", we have taken as a comparison Irish people migrating to England. The British and Irish populations have many features in common: the same language, the same skin color, a short distance but some cultural differences between the two countries. Several studies have found a middle incidence rate for the Irish people compared to the incidence rates of the White British and Black Caribbean people in the UK. For example, Coid found a RR of 1.6 (95% CI 1.1-2.4) for the first-generation Irish immigrants and a RR of 2.3 (95% CI 1.2-4.3) for the first-generation Afro-Caribbeans immigrants (Coid et al. 2008). The same pattern was also observed by considering the relative risks in the second generation immigrants of these two populations. Another study that noted. Fearon, in the AESOP study conducted in 2006, finds a RR of 1.6 (95% CI 1.1-2.2) for the Irish population and higher for other ethnic groups (Fearon et al. 2006) and this gradient of incidence rates was still found when area-level factors were taken into account (Kirkbride et al. in 2007).

These increased rates could be the result of an excess of risk factors in the migrant populations that occur to differing extents in the different groups. Alternatively or in addition there could be specific factors such as the experience of prejudice or discrimination.

In an effort to start to identify the causes of differences in the incidence rates of psychosis observed in our three study groups we investigated the distribution of the main known environmental risk factors.

In internal migrants we observed a significantly higher presence of unemployment, single status, living alone and cannabis abuse. These differences are more clearly visible in the comparison between internal migrants and external migrants, rather than between internal migrants and natives. Regarding the external migrants there was no higher prevalence of any of the risk factors studied. Other socio-environmental risk factors at individual and area levels were unfortunately not available in the present study, social class ,social capital, the expectations toward the migration project and the achievements after migration, ethnic density at the neighborhood area where they live, racism and perceived discrimination are needed (Boydell et al, 2001; Broome et al. 2005; Morgan et al. 2007).

In this study there were no significant differences regarding the age at first contact, DUP, diagnosis and pathway to care between the three groups considered. These results make us conclude that the care system in Bologna is able to provide equitable access paths to treatment even for the less socially integrated groups in our area and those more exposed to known risk factors for psychosis.

5.6 Limitations

We could not test the impact of the risk factors in a multivariable model owing to the limitations of the population data. Furthermore we did not have population level socio-environmental risk factor information such as social class, social capital or measures of social attitudes towards the different migrant groups. Further studies utilizing a case control design or in populations with population risk factor prevalence data available as the EUGEI Project (van Os et al, 2010) funded by the CE in the FP7 program, will be essential to understand this phenomena further.

5.7 Conclusions

Rates of psychosis were considerably and statistically significantly elevated in internal migrants as well as in migrants from outside Italy. This is the first time this phenomena has been demonstrated in modern times. The internal migrant population had significantly higher unemployment, single status, people living alone and cannabis abuse, which could explain at least part of the excess of psychosis in this group. Furthermore, the relationship found between internal migration and psychosis incidence adds evidence as to the role of migration itself (versus ethnicity) on the risk of psychosis.

Chapter 6: Study 3- "First Episode Psychosis course: results from a 1 year follow-up study in Bologna"

6.1 Background of the study 3

If a history of migration itself, and not genetic/ethnic predisposition, is responsible for the higher incidence rate found in migrants, we supposed migrants would have better outcomes compared with non-migrants. This hypothesis was also supported by the baseline observation that migrants with FEP had a lower rate of adverse social characteristics and substance use (which are well known negative prognosis predictors) compared to non migrants. Moreover, starting from our baseline observation of a worse clinical presentation of substance abusers (who were younger and more frequently hospitalized compared to non abusers) we hypothesized that substance abuse at baseline could be an independent risk factor of a worst FEP clinical course.

The third study I present here (Tarricone et al., 2014[3]) aims to evaluate the clinical and social course of an incidence sample of First Episode Psychosis in Bologna West (Northern Italy), recruited from January 2002 to December 2009. Particularly we hypothesized that substance use at the psychosis onset would be an independent risk factors for worse outcomes after adjusting for possible confounders.

6.2 Introduction

Evidence has accumulated that several environmental factors increase the risk of an individual developing psychosis (van Os & Kapur, 2009). In particular, across time and place, including our own study conducted in Bologna (Tarricone et al., 2012), First Episode Psychosis (FEP) onset is associated with substance use, especially cannabis (Arsenault et al., 2002; van Os et al., 2002; Di Forti et al., 2009; Di Forti et al., 2013 In Press)

Some studies have shown that substance use is related to poorer outcome, with lack of adherence to medication, high number of drop outs and a high rate of relapse (Crebbin et al., 2009; Malla et al., 2009). However, it is not clear if substance use is an independent risk factor

[3] Tarricone I, Boydell J, Panigada S, Allegri F, Marcacci T, Minenna MG, Kokona A, Triolo F, Storbini V, Michetti R, Morgan C, Di Forti M, Murray RM, Berardi D. (2014) The impact of substance use at psychosis onset on First Episode Psychosis course: results from a 1 year follow-up study in Bologna. Schizophr Res.;153(1-3):60-3.

for a worse outcomes or if other factors associated with substance use as well as with poor FEP outcomes , such as male gender (Ceskova et al., 2011; Chang et al., 2011; Bertani et al., 2012; social adversity (being single, unemployed, less educated and living alone) (Boydell et al., 2013), are responsible for the unfavorable outcome.

Our study aimed to evaluate the clinical course of an incidence sample of First Episode Psychosis in Bologna West (Northern Italy), recruited from January 2002 to December 2009. Particularly we hypothesized that substance use at the psychosis onset would be an independent risk factors for worse outcomes after adjusting for possible confounders.

6.3. Materials and method

This study is part of the Bologna West First Episode Psychosis project (Bo-FEP) based in Northern Italy. As described in our previous work (Tarricone et al, 2012), Bo-FEP is a naturalistic incidence study that included all patients aged between 18 and 64 years, at their first episode of psychosis, who had a contact with one of the three Community Mental Health Centres (CMHCs) of the West Bologna area (CMHC “Nani”, “Tiarini” and “Scalo”) from January 2002 to December 2009. The Bologna West CMHC runs the Bo-First Episode Program for optimal management of first onset psychosis patients within the general outpatient mental health service.

The inclusion criteria are based on those used in the WHO study (Jablensky et al, 1992): i.e., presence of hallucinations, delusions, thought disorders, bizarre or disturbed behaviors, negative symptoms, mania, or clinical suspicion of psychosis; absence of an organic cause or profound learning disability; and no previous contact with psychiatric services for psychotic symptoms.

Case notes were used to complete the Item Group Checklist (IGC), part of the SCAN (Schedule for Clinical Assessment of Neuropsychiatry, Version 2.1, World Health Organization-Division of Mental Health, Geneva 1998), to collect symptom-related data at the time of presentation and one month later to ensure that cases met ICD-10 criteria for psychotic disorders. Diagnoses were allocated by consensus agreement from a panel of psychiatrists at each study centre and the clinical researcher who completed the ICG-SCAN. We considered 4 diagnostic groups: 1) affective psychoses (ICD F30-F33), 2) non-affective psychoses (ICD10

F20-29), 3) schizophrenia (ICD10 F20, including schizoaffective disorder F25), and 4) substance-induced psychoses (SIPs) (ICD10 F10-F19).

Age of onset was collected by asking the patients and/or key informants about when s/he experienced the first psychotic symptoms as defined above. Date of first contact with services was defined as the date when he/she was referred for the first time to Bologna West CMHC for his/her first episode of psychosis. For each participant, use of drugs was systematically derived from clinical charts and the psychiatrists responsible for the patients. The frequency of cannabis use and other drugs were recorded using the categories available from the Cannabis Experience Questionnaire's (CEQ) items (Barkus et al., 2006; Di Forti et al, 2009). Subjects who used drugs "few times each month" or more frequently in the month before their first experience of psychotic symptoms, were all combined in the same "current user" category, to prevent loss of statistical power.

6.3.1 Study design

We carried out a 12 month follow-up of an incidence cohort of FEP patients collected from January 2002 to December 2009. Operational definition of remission based on case notes data was used (Bebbington et al., 2006). Psychiatric hospitalizations (number and kind of psychiatric hospitalization - compulsory and voluntary-) were considered as indicator of relapse and were evaluated from the clinical charts and from the local computerized information system (SIT); then this information was discussed with the clinicians responsible for the patient.

As an indicator of social functioning and outcome, we investigated employment/study status. Full time study was considered employment. The social indicators were evaluated from the clinical charts and from the local computerized information system (SIT); then this information was discussed with the clinicians responsible for the patient. We analyzed the following indicators of social outcomes:

- interruption of work or study activity at psychosis onset (that is not working or studying for more than 2 weeks);
- resumption of work or study activity after the interruption due to psychosis' onset;
- employment status at 12th month.

6.3.2 Statistical Analyses

We initially used univariate analysis (chi square test for categorical data, Fisher's exact test for categorical data with small numbers or Wilcoxon signed rank test for nonparametric data) to study the associations between psychiatric hospitalizations, social outcomes (interruption of work/study activities; return to work/ study activities; work/study at 12^{th} months) and baseline variables. These variables were gender, age, place of birth, marital status, education, housing, occupational status, psychiatric diagnosis, DUP and substance use. In a multivariate logistic regression analysis we adjusted the associations found for age, gender and all the statistically significant effects identified in first univariate analysis testing the addition of each factor using the Likelihood Ratio Test. Data were analyzed using SPSS for Windows Version 14.

6.4 Results

6.4.1 Sample description

One hundred sixty three patients were recruited at the baseline. The sample's socio-demographic and clinical characteristics at baseline are described in detail in chapter 3. 56 % were male , showed a mean age at onset of 30 years, were on average one year older at first contact with the CMHC (31 years ± 9.4) and 39 (24%) were migrants. They were mainly single (72%); 46% had a high school diploma, 43% were employed and 54% still lived with their family of origin. 80 % had a DUP < 1 year and 41% received the ICD-10 diagnosis of Schizophrenia.

About one third of the sample (n 50, 31%) abused substances; they were all younger than 35 years of age (43% among patients younger than 35 years). Among substance users, 74% used cannabis (n 37), 44% (n 22) alcohol, 32% (n 16) stimulants or hallucinogens and 12% (n 6) opioids. More than half of the substance users were multidrug-users (n 26, 54%)

Users were significantly younger at psychosis onset (24.8 ±4.7 v. 33.0 ±9.8 years, $p<0.0001$) as well as at the first contact with the mental health services (25.3±4.6 v. 33.6±9.9 years, $p<0.0001$). FEP substance users were more frequently male. After adjusting for age and gender, patients with substance use were 2.8 times more likely to be native Italians.

As described in our previous study (Tarricone et al., 2012), among the substance users, 23 received a simple diagnosis of Substance-Induced Psychosis (F10-19); 27 received a dual

diagnosis of non-affective psychosis (F20-29, n=22) or affective psychosis (F30-33,n=5) and substance-related disorder (abuse or dependence).

For all psychoses, the mean age at the onset and at first contact was significantly younger for men but not for affective or substance-related psychosis.

6.4.2 Clinical course

The clinical course of the sample is reported in Table 6.1

Table 6. 1 – clinical course at 12 months follow-up (* p≤0.05; ** p≤ 0.001)

	Substance users	Not substance users
No more in contact with psychiatric services	10 (20%)	18(16%)
▪ Drop-out	5(10%)	8(7%)
▪ Return to Country of origin	3 (6%)	7(6%)
▪ Discharged because recovered	1 (2%)	3(2.7%)
▪ Transfer for territorial jurisdiction	1(2%)	-
One or more Hospitalizations	32 (64%)	18(36%)**
▪ compulsory hospitalization	17(35%)	14(45%)**

One hundred thirty five patients (83%) were still receiving care at 12 months. Four patients (2%) achieved recovery from FEP as judged by the clinicians who had been in charge of the patients according to the Selten et al. (2007) criteria (absence of psychiatric symptoms and function on the pre-morbid level) and were discharged; 10 (6%) returned to their country of origin, 1 was referred to another CMHC for territorial jurisdiction and 13 (8 %) stopped treatment without the clinician's agreement (drop-out). After the onset and during the 12 months follow-up 13 patients (26% of the substance users) stopped substance-use. Fifty nine (36 % of the sample) required hospitalization at some point during the 12 months CMHC outpatient treatment.

Men showed a trend for a higher prevalence of hospitalization (39, 42% vs 20, 28%, c sq= 6.5, p=0.061) and a significantly higher prevalence of compulsory admissions (24, 26% vs 7, 10%, c sq=7.0, p=0.008) compared to women. After adjusting for age, this association was not significant (table 2). Single patients showed a higher prevalence of hospitalization (52, 40% vs 7, 19%, c sq=5.61, p=0.018) than others. After adjusting for age and gender, the association was at trend level (table 2). Finally, patients with a DUP < 1 years showed higher prevalence of hospitalization (52, 40% vs 5, 20%, c sq=3.61, p=0.058) that did not quite reach statistical significance (Table 6.2). No other variables (place of birth, living alone, to be unemployed, lower education, psychiatric diagnosis) were found to be associated with hospitalizations during the 12 months follow-up.

Table6. 2. Predictors of clinical course at 12 months follow-up . Results from logistic regression models [a]

	Hospitalization (Y vs N)	
Predictor	OR adj (95% CI)	p-value
Male	0.980 (0.943-1.018)	0.293
Migrants	0.975 (0.940-1.012)	0.177
Worker	1.261 (0.624-2.549)	0.519
Single	*2.464 (0.935-6.493)*	*0.068*
Living Alone	0.915 (0.294-2.845)	0.878
Education *(≤8 vs >8)*	0.870 (0.440-1.719)	0.689
Substance abuse	**6.491 (2.868- 14.689)**	**≤0.001**
Schizophrenia	1.191 (0.616-2.304)	0.604
DUP *(<1 year vs >1 year*	*0.387 (0.135-1.111)*	*0.078*

, Yes; N, No; OR, Odd Ratio; CI, Confidence Interval
[a] Adjusted for age and gender

6.4.3The impact of Substance use

During the 12 month follow-up period, substances abusers were significantly more likely to be hospitalized than non-abusers (32, 64% vs 27, 24%, c sq=24.1, p≤0.001). Furthermore patients who stopped using substances after the onset showed a significantly higher rate of hospitalizations compared to non-abusers (8, 61 % vs 27, 24%, c sq= 8.2, Fisher's Exact Test 0.008). The odds of hospitalization was six times greater for abusers than for non-abusers after adjusting for age, gender, being single and DUP<1 year (OR 5.84, 95% CI 2.44-13.97, p≤0.001). The percentage of substance abusers who were compulsory hospitalized was significantly higher than that for non-abusers (17, 35% vs 14, 12%, c sq=10.99, p≤0.001), with an OR of 4.19 (95% CI 1.57-11.18, p=0.004) after adjusting for age, gender and being single.

Other predictors tested for both hospitalization and compulsory hospitalization did not improve the models.

6.4.4 The impact of Migrant status

Migrants did not show a different clinical course compared to non migrants, but showed a better social course. Migrants who suspended the work or study activity were significantly more numerous than natives: on a total of 26 active migrants, 14 (58%) suspended their activity at the onset, against only 22 (31.8%) natives from a total of 70 who were working at the onset (c sq=5.2, p= 0.02). In the multivariate logistic regression, adjusted for gender, age and for socio-demographic differences between migrants and natives at the onset (working status, marital status and residential status), the odds for migrants to suspend the work activity is four times greater (OR 3.69, 95% CI 1.29-9.95, p=0.014). However, a significantly higher percentage of migrants returned to work compared to natives at 12th month follow-up (9, 64% vs 8, 40% ; c sq=8.6, p=0.003) (OR 4.57, 95% CI 1.39-15.01, p= 0.012). (table 6.3)

Table 6.3 Work situation before, during and after the FEP	
Work/study before the FEP (total sample N=163, missing 1)	*96 (58.9%)*
Males 54 (58.7%)	Females 42 (60%)
Natives 70 (56.9%)	Migrants 26 (66.7%)
Abusers 31 (62%)	Non abusers 65 (58%)
Schizohprenia 37 (55.2%)	Other Psychosis 59 (62.1%)
Activity Interruption at FEP (economically active sample N=96, missing 5)	*36 (36.5%)*
Males 20 (38%)	Females 16 (40%)
Natives 22 (31.8%)	Migrants 14 (58.3%)*
Abusers 12 (40%)	Non Abusers 24 (38.3%)
Schizophrenia 14 (40%)	Other Psychosis 22 (38.2%)
Return to activity (sample which has interrupted activity at FEP N=36, missing 2)	*17 (47.2%)*
Males 9 (47.4%)	Females 8 (53.3%)
Natives 8 (40%)	Migrants 9 (64.3%)*
Abusers 4 (40%)	Non Abusers 13 (54.2%)
Schizophrenia 6 (42.9%)	Other psychosis 11 (55%)
Work / Study 12 months after FEP (sample still into care N=149, missing 8)	*75 (46%)*
Males 43(55.8%)	Females 32 (50%)
Natives 58 (53.2%)	Migrants 17 (53.1%)
Abusers 22 (51.2%)	Non Abusers 53 (54.1%)
Schizophrenia 27 (44.3%)*	Other psychosis 48 (60%)
(%) refers to the sample above cited, respectively N=163, N=96, N=36, N=149.	

6.5 Discussion

We found that substance abuse at psychosis onset is an independent risk factor for worse clinical outcomes. The course was worse for those who abuse substances as they had more voluntary and compulsory hospitalizations. The worse clinical course for substance

abusers agrees with the literature, where the relationship between substance abuse and worse outcome is evident in terms of therapeutic relationship instability, non-adherence to therapy, and greater number of hospitalizations (Malla et al., 2008; Crebbin et al., 2009; Miller et al., 2009); our evidence demonstrated that this relationship also holds in Italy.

In our study other socio-demographics and clinical characteristics were also found to be associated with clinical outcomes. Male gender and single status were, not surprisingly, found to be associated with higher degree of hospitalizations during the first year FEP follow up. Previous reports have almost consistently showed that those factors are related to poorer outcomes (Singh et al., 2000; Jobe & Harrow, 2005; Boydell et al., 2013).

Our study adds to previous evidence showing the independent effect of substance abuse on FEP course. Substance abuse seems to be a risk factor, particularly affecting male, native Italian, patients, that universally worsen the FEP course.

To our knowledge this is one of the few follow-up studies of an incidence cohort of FEP patients encompassing first generation migrants, whereas previous studies on FEP outcomes evaluated well established ethnic minorities. We found that migrant status is associated with a more unfavorable outcome in the acute phase, in terms of higher rate of loss of work activities. However in the post acute phase migrants showed better social functioning with a higher degree of return to work and work activities. Migrants' socio-demographic characteristics at the onset, such as the better pre-morbid functioning (they are more often married, employed and living outside the family of origin compared to native Italians), along with the evidence of a better social course of FEP in first generation migrants compared to Italian natives suggest lower biological vulnerability and higher psycho-social causation of FEP among first generation migrants compared to natives.

Only 2 previous studies reported a better outcome for ethnic minorities (McKenzie et al, 1995; McKenzie et al, 2001), while the majority reported worse functional outcomes for migrants. For instance, the study by Bhugra et al. in the UK (1997) underlined a worse outcome at 12 months follow-up in the 60% of Afro Caribbean people, in comparison to the 24% of white British people. The worse outcomes, in that case, consisted of relapses, suicide attempts, incomplete remission or a psychotic episode during the remission period (Bughra et al, 1997).

At the other hand, our results are consistent with previous evidences showing higher functioning predicts better outcomes in first episode psychosis patients (Amminger et al., 2011).

Our new finding of a more severe course in the acute phase, followed by better performance of social functioning in the post acute phase, could depend on several factors, related to the migrant population gathered by our CMHC and to the service. Our migrant population is entirely first generation, and particularly burdened by social stress and adversities, as other studies showed (Tarricone et al, 2009; Tarricone et al., 2011). With regard to the factors related to the service and to the psycho-social interventions, the presence in the West Bologna CMHC of a specialized services to understand the migrant's psychological distress (the University Center of Study and Research George Devereaux-Bologna Trans-cultural Psychiatric Team) (Tarricone, Stivanello, 2012) could have contributed to the better outcomes found in migrants. Interestingly, the more positive outcomes found in migrants were not reduced when we adjusted for schizophrenia diagnosis that was generally found to be related to a worse social course.

6.6 Strengths and limitations

Despite the lack of information on severity of psychopathology and persistence and characteristics of substance abuse, we have provide good quality data through an ongoing research project. Diagnosis and substance abuse were recorded by interviewing patients and treating psychiatrists and by searching on the case notes according to well validated research instruments; moreover hospitalization rate is consistently treated as a proxy outcome measure of psychotic disorders course (Addington et al., 2013) Our study has the advantage that our sample is an incidence cohort of FEP patients, and the follow-up rate is high (91%) and therefore well representative of FEP patients. We limited the analysis to individual social risk factors and we did not consider a range of potential pre-morbid and familiar risk factors. We did not consider area-level risk factors (e.g. urbanicity and ethnic density), but we think that this does not compromise our results because we carried out the study in a small and homogeneous area (West Bologna, described in our previous paper, Tarricone et al. 2012).

6.7 Conclusion

The identification of potentially modifiable environmental predictors, such as substance abuse, on the course of the illness and of a specific group of patients who more frequently present this factor, such as native-young-men in Bologna, allows us to envisage a preventive approach to chronicity in psychotic disorders. The present study does not allow direct explanations of the better psychosis course found in migrants. We could hypothesize, along with the socio-developmental model (Morgan et al., 2010), that an average first generation migrants have a FEP only when the burden of adverse psycho-social factors reaches a higher threshold than for natives because they are a particular resilient population, as other studies showed. Thus, the better social course of FEP migrants (as the higher rate of work resumption) could possibly imply that their FEP has a larger “psycho-social causation” compared with FEP in native Italians. On the same conceptual framework we could also hypothesized that psychosocial interventions are more effectives on migrants, considering their larger social causation of psychoses.

Chapter 7: Overall discussion, conclusion and implications

7.1 Key Findings

The Bo FEP study conducted in Bologna, Italy is the first incidence study carried out in Italy on prospectively identified and evaluated individuals with a FEP. We found an overall incidence rate of psychosis of 16.4 per 100,000. Bo-FEP study adds to the previous literature:

1) showing the higher incidence of psychosis in first generation migrants also occurs in Italy;
2) showing that internal migrants have an higher incidence rate of psychosis compared to natives who have not migrated internally and similar to the psychosis incidence rate found for external migrants;
3) the higher incidence rate found in external migrants is not explained by a higher degree of social disadvantage (such as unemployment, never being married, living alone or substance use) compared to natives. The significantly higher incidence in internal migrants however, is associated with a higher degree of social disadvantage, such as never being married and substance use compared to external migrants and to be living alone compared to natives;
4) Substance use and not the status of first generation migrant are associated with worse outcomes at 1 year follow-up, while migrants showed better social outcomes (higher rate of return to work) .

7.2 Methodological consideration (strengths and limitations)

The studies reviewed and presented in the literature review were mostly conducted with a rigorous methodology using new cases and often included healthy controls, using strict definitions of ethnicity, well defined catchment areas and research instruments and interviews that are cross-culturally validated. Therefore, these studies have the potential to be informative about risk factors for FEP in migrants, although in many cases their design cannot be definitive on a causal role of these factors.

However, it should be noted that the studies reviewed adopted different methodologies (study design, case ascertainment, range of instruments, etc) making statistical comparison and drawing definitive conclusions difficult. Moreover, studies conducted with the specific aim of understanding predictors of psychosis in migrants are few, overall conducted in Northern Europe and focus on the post-migration risk factors. None of the studies reviewed considered the psychosis risk inherent to internal-migration.

To my knowledge, the Bologna FEP study is one of the first investigations of prospectively ascertained and clinically assessed first episode cases of psychosis in Italy and included internal migrants. This is a CMHC-based incidence study capturing all potential cases who made contact with mental health services within the catchment area and leakage studies were conducted to minimize under-ascertainment. Some cases completely covered by the private sector (probably milder cases) may not have been included in the study. In Bologna, the public service is widespread across the territory and involves partnerships with private psychiatry. We must also remember that, as stipulated by the organization of Italian CMHCs, patients with psychosis are not seen solely by the GP, but always in collaboration with a CMHC psychiatrist. Usually FEP patients are not treated at only primary care level, however some cases might have been missed, particularly those with less severe psychopathology and a higher socio-economic position who tried to avoid the public health services and seek care in the private sector. Although a great effort was made to identify all potential cases of FEP, some possible underestimation of FEP incidence in the Bologna West catchment area might have occurred. Cases that did not access CMHC directly or by GPs or other services referrals could be underestimated, because we only performed a post-hoc linkage study based on data available in Bologna Mental Health Department (MHD). Consensus diagnoses were performed blind to the ethnic status of the case, therefore minimising observer bias and misdiagnosis.

Acknowledging that the true dynamic population at risk over the survey period may have varied slightly, denominators for the population at risk of psychosis were derived for each year from the Municipality Registry. There is no reason to believe that there was any systematic bias or under-enumeration of minority ethnic groups, male, and younger people. We minimized any misclassification of ethnic status in either our denominator or our

numerator populations by using a dichotomous ethnicity variable with a very broad MI group and an easily definable comparator group.

Despite the lack of information on severity of psychopathology and persistence and characteristics of substance abuse, there was good quality data through an ongoing research project. Diagnosis and substance abuse were recorded by interviewing patients and treating psychiatrists and by searching on the case notes according to well validated research instruments; moreover hospitalization rate is consistently treated as a proxy outcome measure of psychotic disorders course (Addington et al., 2013) This study has the advantage that the sample is an incidence cohort of FEP patients, and the follow-up rate is high (91%) and therefore well representative of FEP patients. The analysis was limited to individual social risk factors and did not consider a range of potential pre-morbid and familiar risk factors. Area-level risk factors (e.g. urbanicity and ethnic density) were not considered, but this does not compromise the results because the study was carried out in a small and homogeneous area (West Bologna, described in my previous paper, Tarricone et al. 2012). The impact of the risk factors could not be tested in a multivariable model owing to the limitations of the population data. Furthermore there was no population level socio-environmental risk factor information such as social class, social capital or measures of social attitudes towards the different migrant groups.

7.3 Comparison with other FEP studies

Overall the IR of FEP found is lower than the IR previously found by other studies carried out in UK (Kirkbride et al, 2006; Coid et al., 2008; Cheng et al, 2011) and in other northern Europe countries (Cantor-Grae et al., 2005; Lao et al 2006; Veling et al., 2006). A direct statistical comparison between the results of our study and previously studies was not performed but the incidence we found seems to be quite near the incidence found in Bristol (Kirkbride et al., 2006) and in South Cambridgeshire (Cheng et al., 2011), both overall and for the youngest groups (18-36 years old) particularly for schizophrenia. Overall Bologna is less deprivated and ethnically mixed than many European areas where other studies have been conducted. For instance, Bologna is an urban area with a high degree of social cohesion and low population mobility. The distribution of putative social risk factors for psychosis varies with the different population-groups. Although the Bologna population is

among the oldest in the world, with one in four citizens older than 65, migrants and students are two younger groups characterized by much greater economic instability and lower social cohesion than is found among Bologna's other inhabitants (Provincia di Bologna, 2007). Thus the low overall rates mask higher rates in these groups. Bologna is a recent focus of immigration and most of the migrants living in this area are first-generation young migrants at the beginning of their adaptation process to the host society. Interestingly, we found an IR similar to the IR found in Brazil, Sao Paolo (Menezes, et al., 2007). The incidence found in the Sao Paolo study was actually lower than expected in such a vast urban area. In this regard, Kirkbride & Scoriels (2009) stated that socio-environmental processes involved in the aetiology of schizophrenia seem to be more complex than simple linear associations with urbanicity. Social organisation, for example the prevalence of people living with families and level of social cohesion, should evaluated by further studies to try to explain similarities in psychosis rates among those studies.

However, within the context of an overall lower incidence of psychoses, the Bologna study found the same socio-demographic correlates of incidence, such as age, gender and ethnicity, as found in northern European studies. Similarly it confirmed the age-at-first-contact pattern previously observed for schizophrenia (Hafner et al., 1993; Kirkbride et al., 2006): i.e. the classic excess for men at younger ages, followed by a later decline, with a non-significant rise in the incidence of psychoses for women older than 40. There was a greater incidence of schizophrenia and SIP for men than for women, as found by previous studies (Aleman et al, 2003; Kirkbride et al., 2006). Like Kirkbride et al. (2006), the Bologna study confirmed that the commonest time of onset for affective psychosis is in early adulthood, as in schizophrenia, but the pattern for men and women is much more similar. The higher risk for FEP found among MI is consistent with the mean weighted incidence rate ratios (2.3, 95% CI 2.0-2.7) found in the recent meta-analysis of Bourque et al (2001). It is important to note that despite incidence variation across countries, the IRR for first generation migrants seems to be a constant proportion (around 2). This ratio probably implies a "history of migration x environment" interaction model.

7.4 Key findings in relations to hypotheses formulated

The Bologna study observed a 2.5 times increased incidence of psychoses in the MI group compared with the NA group, consistent with the result of the meta-analyses of Bourque et al. (2011). These results of the BoFEP Study together with those of previous studies reviewed allows postulation that migration should be considered as a dimension with different levels of exposure to risk factors for psychosis. Early age of migration, higher duration of stay in the host countries, to be a foreign migrant or second generation migrants with both parent born abroad, to be labour migrant unemployed in the host country and to live in a low ethnic-density urban area seem to be the conditions faced by migrants and relatively specific to migrant status that could expose them to the highest level of isolation and perceived “otherness”, two well-known associations with psychosis.

The Bologna First Episode Psychosis Study findings seem to reinforce the hypothesis that the excess of psychosis found in first generation foreign migrants is much more related to subjective experience of discrimination, than to ethnicity and to objective social disadvantages or substance use. Those factors were under represented in external migrants; the only factor significantly more frequently found in FEP internal migrants compared with natives was living alone. In the BoFEP sample, FEP MI seem to have a higher level of social functioning: a higher proportion are workers and live outside the parental family, in contrast to natives. These findings could indicate that socio-environmental risk factors not included here (such as individual social class and social capital; psychological effects such as life events, achievements, and expectations; and neighbourhood deprivation) (Broome et al, 2005; Morgan et al., 2007b) could be relevant, following the socio-developmental model of Morgan et al (2010). The other relevant finding coming from the review of the studies identified is that ethnicity, as well gender are not fixed variables with an attributable risk-value across different places and times: in several paces black people are more at risk, in some others, East European or North African are at higher risk to develop psychosis. At the same way, some studies found young immigrant males at higher risk and some others females. Thus, considering the history of immigration and emigration with regard to each country were migrants came from and settle seems to be crucial in order to understand this heterogeneity. Thus, it's very intriguing to understand what are those characteristics of each specific host society that interact with each specific

type of migrants and ethnic minorities (first-or next-generation; economic migrants or political migrants, etc.) to increase the risk of psychoses. It seems necessary to look for the risk of psychosis in the "immigrant status" rather than in the "migrants": "Immigrant status" signifies the special meeting between the migrant and the host country and the nature of this meeting could explain the psychosis risk for migrants in different countries.

Finally, the study found that the better social functioning at baseline in migrants was also associated with better social outcomes. Better social functioning at baseline and better social outcomes could be related to less social-cognitive impairments in FEP first generation migrants and this hypothesis could be elucidated by studies involving social and cognitive measurements. Moreover, the follow-up study adds to previous evidence showing the independent effect of substance use on FEP course. Substance use seems to be a factor, particularly affecting male, native Italian patients, that universally worsens the FEP course.

7.5 Implications of findings and future work

The Bologna FEP study found that the incidence of schizophrenia and other psychotic syndromes varies according to age, gender and migrant status. Thus, this study adds a contribution to our understating of the role of the major environmental candidates in FEP, such as gender, age, ethnicity, substance use and social organisation which seem to be pathogenic in Italy as well as in Northern Europe. Interestingly, despite incidence rate variations of psychosis, IRR for migrants compared to natives are quite stable over time and place.

The identification of potentially modifiable environmental predictors, such as substance abuse, on the course of the illness and of a specific group of patients who more frequently present this factor, such as native-young-men in Bologna, allows us to envisage a preventive approach to chronicity in psychotic disorders.

These findings have implications for policy and mental health service development, since it seems possible to develop targeted prevention intervention for risk groups, such as youth, migrants and substance abusers. In keeping with the AESOP Study (Morgan et al., 2006), the Bologna study did not find any evidence that the DUP was longer for MI patients than

for NA patients. In this study there were no significant differences regarding age at first contact, DUP, diagnosis and pathway to care between the three groups considered. These results are different from those found by studies in UK. In the UK, research has consistently shown that black Caribbeans are not only at greater risk of developing psychosis, but are also more likely to access mental health care via adversarial routes, often involving the police and compulsory admission, and more likely to be treated in secure and forensic settings (Morgan et al, 2006). The authors of the AESOP study (Morgan et al., 2006) conjecture that there are ethnic differences at first contact, and consequently that processes within these communities might increase the risk of an adverse pathway to care prior to contact with services. This hypothesis needs further clarification in future studies. Probably in Bologna the first generation migrants have a different approach to and experience with services than those found in UK for ethnic minorities. The results lead to the conclusion that the care system in Bologna is able to provide equitable access paths to treatment even for the less socially integrated groups in our area and those more exposed to known risk factors for psychosis.

The specificity of the Bologna results also sets the scene for future investigation using more detailed assessments of individual and geographical characteristics with a view to examining causation. We need further studies to elucidate which pre-migration and migration characteristics could interplay with post migration adverse cultural and social factors and biological predisposition in causing high incidence rate of psychosis in migrants. Further studies, with population based control groups for comparison, such as the recently started pan-European EUGEI (European Network of National Schizophrenia Networks Studying Gene Environment Interactions), funded by the CE in the FP7 program, will allow a deeper understanding of psychosis causation-mechanisms(van Os et al, 2010).

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Table 1. 1 Characteristics s of included studies

Authors, year of publication, country	*Study design, setting and sample source, diagnostic assignment classification and ethnic definition*	*Sample: size, gender, age, ethnic composition, migrants' generation*	*Incidence and Risk Factors for psychosis in migrants*
All setting (outpatients, inpatients, GPs, etc) –41 studies			
Cantor Grae & Pederesen, 2013 Denmark	Danish population-based cohort study Period: All persons born between January 1, 1971, and December 31, 2000 (N=1 859 419) residing in Denmark by their 10th birthday with follow-up data to December 31, 2010. Case identification Persons were followed up from their 10th birthday for the development of mental disorders based on outpatient and inpatient data and linked with Danish Psychiatric Central Research Register Diagnosis Assignment-Classification: ICD-8 and ICD-10 (full spectrum of possible mental disorders) Ethnic definition: Foreign migration background was classified according to thevperson and his or her parents' country of birth, as well as the mother's country of residence at the time of the person's birth. Population at risk: The Danish Civil Registration System	Schzophrenia • **Foreign-Born Adoptees** Men 3.77 (2.99-4.76), Women 1.95 (1.50-2.53) • **First-Generation Immigrants** Men 3.07 (2.53-3.71), Women 1.24 (0.89-1.71) • **Second-Generation Immigrants** • **By Mother Only** Men 1.96 (1.67-2.31), Women 1.32 (1.09-1.61) • **By Father Only** Men 2.23 (1.91-2.60), Women 1.17 (0.94-1.46) • **By Both Parents** Men 2.74 (2.34-3.20), Women 1.41 (0.97-2.06) • **Persons Born Abroad to Danish Expatriates** Men 1.26 (0.82-1.92), Women 1.07 (0.65-1.76) • **Native Danes With a History of Foreign Residence** Men 1.56 (1.21-2.00), Women 0.86 (0.56-1.32) • **Native Danes** Men 1.22 (1.17-1.26), Women 0.81 (0.78-0.85)	All categories of foreign migration background, except persons born abroad to Danish expatriates, were associated with increased risk for at least 1psychiatric disorder. • Foreign-born adoptees had increased IRRs for all psychiatric disorders and had the highest IRRs for these disorders compared with other foreign migration categories. • First- and second-generation immigrants having 2 foreign-born parents had significantly increased IRRs for schizophrenia and schizophrenia spectrum disorders and had similar risk magnitudes. • Second-generation immigrants having 1 foreign-born parent had significantly increased IRRs for all psychiatric disorders. • Native Danes with a history of foreign residence had increased IRRs for bipolar affective disorder, affective disorders, personality disorders, and schizophrenia spectrum disorders. Men had significantly higher IRR than women
Tarricone I, 2012 Bologna, Italy	All first episode of psychosis, aged 18-64, identified among the catchment area of West Bologna. Period: January 2002-december 2009. Case identification: Item Group Checklist (IGC part of the SCAN). Diagnosis Assignment-Classification: ICD-10 F10-39 Ethnic definition: country of birth of the patients and their parents Population at risk: Municipality Registry	163 cases(71F) Mean age at onset: 30.5 Ethnicity: Native124 (76.1%) Migrants 39 (23.9%) Generation: all migrants were first-generation	IRR for migrant (all psychoses) 2.530 (95%CI_ 2.170-2.890). Migrants compared to natives were significantly more likely to be **working** (OR 3.761, 95%CI_1.540-9.188) and live outside the family of origin (OR 4.035, 95%CI_1.405-13.189). Migrants compared to natives were **significantly less likely to be substance abusers**
Cheng , 2011 Cambridgeshire, UK	All first episode psychosis, aged 17-35 years, presenting to CAMEO (early intervention in psychosis service) Period: 2002 to 2007. Case identification: Registry – PANSS. Diagnosis Assignment-Classification: ICD-10 :F10-39. Ethnic definition: self-ascription using standard categories. Population at risk: annual mid-term census estimates provided by the	285 cases (89 F) Mean Age: - Ethnicity: WB: 206 (72%), NBW: 28 (9.8%)	Overall crude incidence 50/ 100000 person years (95%CI_44.5-56.2) WB: 47.0 (95%CI_41.0–53.9) NBW 49.4 (95%CI_32.8–71.4) B: 94.2 (95%CI_47.0–168.5) O: 42.5 (95%CI_28.0–61.9) IRR Both sex Men Woman WB: 1.0 1.0 1.0

	Office for National Statistics (ONS)	B: 11 (3.9%) O:27(9.5%) Unknown: 13 (4.6%) Generation: not specified	NBW: 1.1 (95%CI_0.8-1.7)# 1.0 (95%CI_0.6-1.7)# 1.4 (95%CI_0.7-2.6)# **B: 2.1 (95%CI_1.1-3.8)** 1.7 (95%CI_0.7-3.8)# **2.8 (95%CI_1.1-7.1)** O: 0.9 (95%CI_0.6-1.4)# 0.9 (95%CI_0.6-1.5)# 0.8 (95%CI_0.4-1.8)#
Veling, 2011 The Hague, Netherlands	All first episode psychosis, aged 15-54, first contact with a physician (general practitioner, psychiatrist, psychiatry resident) The Hague Period: 1997-1999 and 2000-2005. Case identification: WHO 10-country study criteria (Jablensky et al., 1992). Diagnosis Assignment-Classification: DSM IV Ethnic definition: census information; citizens' country of birth and that of their parents. Population at risk: municipal population register.	Same sample in Veling 2011, 2008a, 2007 and 2006. 618 cases (182F): 273 immigrants 119 II gen. citizens 226 D citizen Mean age: 27.5 years Ethnicity: Dutch: 226 (36.56%*) S: -immigrant: 57 (9.22%*) -II gen. citizen:37 (5.98%*) N.A.: -immigrant: 17 (2.75%*) -II gen. citizen: 4 (0.64%*) T: -immigrant: 37 (5.98%*) -II gen. citizen:18 (2.91%*) M: -immigrant: 68 (11%*) -II gen. citizen: 23(3.72%*) O non W: -immigrant: 72 (11.65%*) -II gen. citizen: 25 (4.04%*) W: -immigrant: 22 (3.55%*) -II gen. citizen: 12 (2%*)	IRR (relative to Dutch citizens): All non-western country: Immigrant: 1.95 (95%CI_1.63-2.33) 2nd gen: 1.82 (95%CI_1.43-2.32) S: Immigrant: 1.77 (95%CI_1.32-2.36) 2nd gen: 2.34 (95%CI_1.63-3.34) Na: Immigrant: 1.69 (95%CI_1.03-2.76) 2nd gen: 1.92 (95%CI_0.71-5.17)# T: Immigrant: 1.38 (95%CI_0.98-1.96)# 2nd gen: 2.39 (95%CI_1.47-3.89) M: Immigrant: 3.43 (95%CI_2.62-4.50) 2nd gen: 4.11 (95%CI_2.65-2.38) O non Western countries: Immigrant: 1.82 (95%CI_1.39-2.37) 2nd gen: 0.91 (95%CI_0.60-1.38)# **Younger** age at the time of migration (<39 years old) Non-Western immigrants migrated between the age of 0 and 4 years (the risk gradually decreased among those who migrated at older ages, except for a Moroccan migrated between ages 15 and 24 years. IRR of psychotic disorder was 5.21 (95%CI_2.67-10.22) for those who migrated before the age of 1 year relative to that Dutch citizens.
Bhugra et al., 2010 London UK	Case control study All first episode psychosis, 18-64 years residing in 2 health districts in London who made contact for the first time with hospital or community services. Period: 1 April 1991-31 March 1993. Case identification: I psychosis screening, WHO; II Present State Examination (Wing et al., 1974) or Syndrome Check List (Wing et al. 1974). Diagnosis Assignment-Classification: CATEGO Program (Wing et al. 1974). CANDID 1 Ethnic definition: self-ascription using the categories developed for 1991 census. Population at risk: 1991 census	Same sample of Bhugra et al., 1997 100 with research diagnosis of schizophrenia 38 white 38 AC 24 As 200 controls	African-Caribbean patients were significantly less traditional than their controls in their use of language, gender roles, contact with relatives, desire to live and work with white people, and desire to spend their leisure time with white people. AC patients compared with their healthy controls, they have a strong desire to live in white areas, to work with white people and to spend their leisure time with them. South Asian patients scored on the borderline of significance for being less traditional than controls on a single section: religion. The difference between the two groups of patients strongly suggests that vulnerable African-Caribbeans may be more prone to schizophrenia because their frustrated attempts to integrate into white society leave them marginalized and distanced from the support offered by their families and other members of their

			ethnic group.
Morgan et al., 2010 South London, UK	Aesop Study. Case-control - MRIstudy; All first episode psychosis people, aged 16-64 years, presenting to mental health services residence within tightly defined catchment areas in South London. Period: 6 year period (1997-2003). Case identification: Screening Schedule for Psychosis (Jablensky et al., 1992). Diagnosis Assignment-Classification: ICD-10 :F20-29; 30-33 Ethnic definition: self-ascription and standardized employing 11 categories used by UK census in 2001 (MRC Socio-demographic Schedule). Ethnic identification was assessed using Candi-1-A(Bhugra et al 1999). People selected if belonging to the following categories: 1) white British; 2) AC, 3) BA Population at risk: Office of Population and Census Statistics Psychiatric Morbidity Survey.	161 patients meeting the criteria, 97 consented to MRI, 75 final sample • 34 white British [male (n=20), mean age 28 years, ICD-10 schizophrenia (n=16), other psychosis (n=18)] • 41 either African-Caribbean (n=23) or black African (n=18) patients [male (n=27), mean age 27 years, ICD-10 schizophrenia (n=23), other psychosis (n=18)]. 68 controls • 33 were white British • 35 either African-Caribbean (n=22) or black African (n=13)	Compared with the African-Caribbean/black African controls, the African-Caribbean/black African patients had a significantly smaller total grey-matter volume [551.4 ml (S.D.=40.8) v. 570.8 ml (S.D.=48.5), f=5.0, p=0.028] and significantly larger third ventricle :brain volume ratio [0.27 ml (S.D.=0.21) v. 0.17 ml (S.D.=0.15), f=4.75, p<0.03].
Reininghaus, 2010 South-east.London, UK Nottingham, UK	Aesop Study. Case-control - Incidence study; All first episode psychosis people, aged 16-64 years, presenting to mental health services residence within tightly defined catchment areas in Nottingham or South-East London. Period: 6 year period (1997-2003). Case identification: Screening Schedule for Psychosis (Jablensky et al., 1992). Diagnosis Assignment-Classification: ICD-10 :F20-29; 30-33 Ethnic definition: self-ascription and standardized employing 11 categories used by UK census in 2001 (MRC Socio-demografic Schedule). Ethnic identification was assessed using Candi-1-A(Bhugra et al 1999). Population at risk: Office of Population and Census Statistics Psychiatric Morbidity Survey.	139 cases (70F), Non-affective psychosis:81(58.3%) Affective psychosis:58 (41.7%) 234 ctr. (131F) Mean age: 31.6 cases, 38.1 ctr Male: 49.6% cases, 44% ctr Ethnicity: WB: 75 (54%) cases 181 (77.4%) ctr BME: 64 (46%) cases 53 (22.7%) ctr	Risk factors: BME with strong ethnic identification OR 2.73 (95%CI_1.22-6.12) In contrast, no significant differences in ethnic identification were observed between WB cases and ctr. The association between strong ethnic identity and psychosis in BME individuals was attenuated and non significant when controlled for perceived disadvantage.
Norredam M, 2009 Denmark	Cohort - Case-control Study Refugees who received residence permission in Denmark from 1.1.1993 to 31.12.1999 were matched 1:4 on age and sex with native Danes (n =116,556). Individuals who were <18 years (n = 18,861) when they obtained residence permission were excluded. Subsequently, all individuals in the cohort who had an inpatients or out patients psychiatric hospital contact in the study period were identified. Period:1-1-1994 to 31-12-2003 (1-1-1995 for outpatients) Case identification: Danish Psychiatric Central Register Diagnosis Assignment-Classification: ICD-10 Psychotic disorder (F20-F-29: schizophrenia, schizotypal and delusional disorder)	Population characteristic: 145 695 Refugees: 29,139 Native Danes (Danish born residents with Danish-born parents): 116.556 Mean age of the cohort: 33 Ethnicity: A: 747(2.6%)	Age standardised Relative Risk: Native Danes: 1 A: 2.78 (95%CI_1.57-4.91) EE(excl Y): 4.81 (95%CI_2.77-8.36) Y: 1.64 (95%CI_1.34-2.00) Ir: 2.30 (95%CI_1.72-3.08) ME(incl. Nord Af): 3.10 (95%CI_2.28-4.21) Sub-Saharian Af: 1.88 (95%CI_1.39-2.56) All refugees: 2.03 (95%CI_1.72-2.40)

	Ethnic definition: country of birth. Population at risk: Statistics Denmark and Statistical Department at the Danish Immigration Service Refugees	EE(excl Y): 555 (1.9%) Y: 15 369 (52.7%) Ir: 4 618 (15.9%) ME(incl. Nord Af): 3 035 (10.4%) Sub-Saharian Af: 4 815 (16.5%) Ethnicity for Cases: Native Danes: 756 A: 16 EE(excl Y): 17 Y:155 Ir: 66 ME(incl. Nord Af): 58 Sub-Saharian Af: 59 All refugees: 371	Geographical subdivision of refugees showed that the risk of having a first-time contact for a psychotic disorder was significantly increased for all refugees compared with native Danes.
Dazzan et al., 2008 South-east.London, UK Nottingham, UK	AESOP study (case-control). Everyone between 16 and 64 who made contact with mental health services because of a first episode of any probable psychosis, non psychotic mania or bipolar disorder in South East London, Nottingham and Bristol. Period: from Sep 1997 to Aug 1999 and the first nine months of this period in Bristol. Case identification: WHO-study criteria Diagnosis Assignment-Classification: -Affective psychoses DSM-IV : 296.X4, 296.4,296.89 -Non affective psycoses DsmIV : 295.XX, 297.XX, 298.8, 299.9 -Schizofrenia DSM IV : 295.XX ; -Substance Induced Psychosis DSM IV 291.3,291.5.,292.11., 292.12 Ethnic definition: ascribed using self-ascription, place of birth and parental place of birth. Population at risk: Office of Population and Census Statistics Psychiatric Morbidity Survey.	468 approached, 310 completed a neurological evaluation (n=146 schizophrenia, n=113 affective psychosis, n=51 other psychosis) 239 controls	There was no effect of ethnicity on any of the neurological soft sign scores (all P40.15). There was also no ethnicity6group interaction for any of the scales (all P40.1). Moreover, participants with psychosis of White ethnicity and of Black and minority ethnic groups had higher neurological soft sign scores than the control group of the same ethnic group (all P-values for total neurological soft signs score 50.001). Therefore, ethnicity does not seem to be a confounding factor in the neurological soft sign differences between those with and without psychosis.
Cooper, 2008 South-east.London, UK Nottingham, UK	Aesop Study. Case-control - Incidence study; All first episode psychosis people, aged 16-64 years, presenting to mental health services residence within tightly defined catchment areas in Nottingham or South-East London. Period : 6 year period (1997-2003). Case identification: Screening Schedule for Psychosis (Jablensky et al., 1992). Diagnosis Assignment-Classification: ICD-10 :F20-29; 30-33 Ethnic definition: self-ascription and standardized employing 11 categories used by UK census in 2001 (MRC Socio-demografic Schedule). Ethnic identification was assessed using Candi-1-A(Bhugra et al 1999). Population at risk: Office of Population and Census Statistics Psychiatric Morbidity Survey.	197 cases (95F) and 285 ctr. (163F), Mean age: 32.1 cases, 38.7 ctr. Ethnicity: Black group(79 cases) BC: 108 (22.4%*) BA: 32 (6.6%*) BO: 2 (0.4%*) White group(118 cases) WB: 305 (63.3%*) OW: 35 (7.3%*)	Black ethnic group OR 4.5 (95%CI_2.7-7.4). Adjusted for: -overall perception of disadvantage OR 4.1 (95%CI_2.5-6.8) -perception of disadvantage due to skin color OR 6.9 (95%CI_3.7-13) - perception of disadvantage due to culture OR 5 (95%CI_3-8.3) - perception of disadvantage due to social class OR 4.6 (95%CI_2.8-7.7) -social class, educational level, employment status and religion OR 3.5 (95%CI_2-6.2) -self-esteem and self-concept OR 7.6 (95%CI_4.1-14.1)

Reininghaus, 2008 South-east.London, UK Nottingham, UK	Aesop Study. Case-control - Incidence study; All first episode psychosis people, aged 16-64 years, presenting to mental health services residence within tightly defined catchment areas in Nottingham or South-East London. Period : 6 year period (1997-2003). Case identification: Screening Schedule for Psychosis (Jablensky et al., 1992). Diagnosis Assignment-Classification: ICD-10 :F20-29; 30-33 Ethnic definition: self-ascription and standardized employing 11 categories used by UK census in 2001 (MRC Socio-demografic Schedule). Ethnic identification was assessed using Candi-1-A(Bhugra et al 1999). Population at risk: Office of Population and Census Statistics Psychiatric Morbidity Survey.	224 cases (102F), 322 controls (191F) Age: 16-29: cases 50.9%, ctr 32.6%; 30-65: cases 49.1%, ctr 67.4% Ethnicity: WB: cases 113(50.4%), ctr 214(66.5%) AC: cases 59 (26.3%), ctr 54 (16.8%) BA: cases 24 (10.7%), ctr 11 (3.4%) OW: cases 11 (4.9%), ctr 34 (10.6%) A: cases 12 (5.4%), ctr 6 (1.9%) O: cases 5 (2.2%), ctr 3 (0.9%)	African-Caribbean cases and controls were more likely to be unemployed than their White British counterparts OR 2.15 (95%CI_1.39-3.33). **Unemployment** was associated with psychosis in both groups to a comparable degree. -WB unemployed OR 2.49 (95%CI_1.54-4.01) -AC unemployed OR 3.2 (95%CI_1.37-7.07) The association of achievements and expectation with case status varied by ethnicity. -WB lower achievement/higher expectation: OR 2.58 (95%CI_1.44-4.61) -AC lower achievement/higher expectation: OR 4.72 (95%CI_1.62-13.80)
Morgan C, 2008 South-east.London, UK Nottingham, UK	Aesop Study. Case-control - Incidence study; All first episode psychosis people, aged 16-64 years, presenting to mental health services residence within tightly defined catchment areas in Nottingham or South-East London. Period : 6 year period (1997-2003). Case identification: Screening Schedule for Psychosis (Jablensky et al., 1992). Diagnosis Assignment-Classification: ICD-10 :F20-29; 30-33 Ethnic definition: self-ascription and standardized employing 11 categories used by UK census in 2001 (MRC Socio-demografic Schedule). Ethnic identification was assessed using Candi-1-A(Bhugra et al 1999). Population at risk: Office of Population and Census Statistics Psychiatric Morbidity Survey.	390 (172F) cases, 391 (230F) controls Mean age: cases 30.5, controls 37.3 Ethnicity: WB: cases 177(45.4%), ctr 245(62.7%) OW: cases 27(6.9%), ctr 37 (9.5%) BC: cases 95 (24.4%), ctr 72 (18.4%) BA: cases 41 (10.5%), ctr 20 (5.1%) A: cases 21 (5.4%), ctr 7 (1.8%) O: cases 29 (7.4%), ctr 10 (2.5%)	Linear relationship between concentrated disadvantage and odds of psychosis. The association between indicators of social disadvantage and case-control status were broadly similar for White British and Black Caribbean subjects. There was no strong evidence that the effect of social disadvantage and isolation was more pronounced in Black Caribbean cases, relative to their controls, than in White British cases, relative to their controls. However there was evidence that, on a number of indicators, **social disadvantage and isolation** were more prevalent in the Black Caribbean population.
Coid JW, 2008 East.London, UK (Three boroughs: City and Hackney, Newham	All first episode psychosis, aged 18 to 64 years, who made contact in three boroughs in East London. Period: 2 year - from 1/12/1996 to 30/11/1998 in city and Hackney;	484 (186F) cases: -362 non affective psychosis -122 affective psychosis	Age and sex adjusted IRR: *Non Affective psychosis* Total sample / First generation / Second generation WO 1.8(95%CI_1.3-2.6) / 1.6(95%CI_1.1-2.4) / 2.8(95%CI_1.5-5.2)

and Tower Hamlets)	- from 1/12/1998 to 30/11/2000 in Newham and Tower Hamlets Case identification: first screen based on WHO study and AESOP study criteria, then underwent SCAN and Personal and Psychiatric History Schedules. Diagnosis Assignment-Classification: DSM-IV:non affective psychoses 295.xx, 297.xx, 298.8 and 298.9; affective psychoses 296.x4, 296.80 and 296.90. Ethnic definition: ascribed by multiethnic panel of researchers using all avaible information, including self-ascription, place of birth, and parental place of birth, the final decision being that of the researcher. Population at risk: 2001 census population of England and Wales stratified by sex and age	Age: 18-24: 143 (29.6%) 25-34: 207 (42.8%) 35-44: 78 (16.1%) 45-44: 39 (8.1%) 55-64: 17 (3.5%) Ethnicity: WB: 112 (23.1%) WO: 66 (13.6%) BC: 90 (18.6%) BA: 83 (17.2%) A: 106 (21.9%) O: 27 (5.6%) Generation: -first-generation: (non UK-born) 240 (49.6%) -second-generation: (UK-born) 244 (50.4%)	BC 4.2(95%CI_3-5.8) 2.3(95%CI_1.2-4.3) 4.9(95%CI_3.5-6.9) BA 3.4(95%CI_2.4-4.7) 3.2(95%CI_2.3-4.6) 3.7(95%CI_2.2-6.4) A 1.7 (95%CI_1.2-2.3) 1.8(95%CI_1.3-2.6) 1.3(95%CI_0.8-2.1)# *Affective psychosis* WO 2.3(95%CI_1.3-4.00) 2.2(95%CI_1.2-3.9) 2.1(95%CI_0.6-6.8)# BC 4(95%CI_2.4-6.9) 3.2(95%CI_1.4-7.4) 4.2(95%CI_2.3-7.7) BA 2.7(95%CI_1.5-4.9) 2.6(95%CI_1.4-4.8) 2.7(95%CI_1.0-7.7) A 1.3(95%CI_0.8-2.3)# 1.6(95%CI_0.9-2.8)# 0.4(95%CI_0.1-1.8)# Asian women but not men of both generations were at increased risk for psychoses compared with white British individuals.
Kirkbride JB, 2008 South London, UK	Population-based cross sectional postal survey of 5% of the relevant adult population in the South London centre of the AESOP study to collect detailed social capital data at neighbourhood level using items from two scales (Sampson et al 1997; McMulloch 2001). Period: January to March 2004 and January to March 2006. Ethnic definition: self-ascription employing 11 standardized categories used by UK census in 2001 (MRC Socio-demographic Schedule). Population at risk: 2001 Census of Great Britain.	4220 subjects (59% women) Age: 16–25: 273 (6.5%) 26–35: 1020 (24.2%) 36–45: 1126 (26.7%) 46–55: 718 (17.0%) 56–65: 418 (11.4%) 66+: 558 (13.2%) Ethnicity W B: 3073 (72.8%) BC: 344 (8.2%) BA: 295 (7.0%) A :122 (2.9%) C: 28 (0.7%) O: 223 (5.3%)	Social cohesion and trust (SC&T) Low IRR 2 (95%CI_1.2-3.3) Medium IRR 1 High IRR 2.5 (95%CI_1.3-4.8) Non linear association between the level of Social Cohesion and Trust (SC&T) at the neighborhood level and the incidence of schizophrenia: the neighborhood with low and high levels of SC&T (Social Cohesion and Trust) had significantly increased rates of schizophrenia compared with median neighborhoods (age, sex and ethnicity were significant individual-level predictors of the incidence of schizophrenia but could not explain variation attributable to neighborhood level factors.) Ethnic density WB BME Lowest third IRR 1 IRR 6.6 (95%CI_3.0-14.2) Middle third IRR 2.3 (95%CI_0.9-5.8)# IRR 4.8 (95%CI_2.0-11.5) Highest third IRR 1.0 (95%CI_0.3-3.4)# IRR 3.8 (95%CI_1.4-10.9)
Veling W, 2008 a The Hague, Netherlands	All first episode psychosis ,aged 15 to 54 years in The Hague Period: 7 years from 1/4/1997 to 1/4/1999 and from 1/10/2000 to 1/10/2005. Case identification: WHO 10-country study criteria (Jablensky et al., 1992). Diagnosis Assignment-Classification: DSM-IV: schizophrenia, schizophreniform disorder and schizoaffective disorder. Ethnic definition: census information; citizens' country of birth and that of their parents. Population at risk: municipal population register.	Were used partly the same sample in Veling 2011, 2008a, 2007 and 2006. Cases: 466 (136F) Age 15-34: 379 (81%) Age 35-54: 87 (19%) Native Dutch: 226 (48.5%*) Immigrants(first and second generation): 240 (51.5%*)	IRR of psychotic disorders for all immigrants together compared with native Dutch and adjusted for age, sex, marital status was 2.22 (CI 1.78-2.76). All immigrants: 2.22 (95%CI_1.78-2.76) -Moroccans 3.69 (95%CI_2.78-4.90) -Surinamese 1.88 (95%CI_1.45-2.44) -Turks 1.75 (95%CI_1.25-2.46) IRR of psychotic disorder in migrants compared with Native Dutch by neighborhood ethnic density was:

		- Moroccans: 91 (37.9%*) - Surinamese: 94 (39.1%*) - Turks: 55 (23%*) Generation: not specified	<u>***Low density:***</u> / <u>*High density:*</u> not significative -All immigrants: 2.36 (95%CI_1.89-2.95) / 1.25 (95%CI_0.66-2.37)# -Moroccans: 4.43 (95%CI_3.28-5.97) / 1.56 (95%CI_0.75-3.21)# -Surinamese: 1.88 (95%CI_1.42-2.5) / 1.19 (95%CI_0.58-2.44)# -Turks: 1.74 (95%CI_1.16-2.6) / 1.12 (95%CI_0.55-2.30)#
Veling W, 2008b The Hague, Netherlands	Case-control study. All first or second generation immigrants from non-western countries (of which 85% from Surinam, Morocco, Turkey, or Netherlands-Antilles), aged 18–54 years, who made first contact with a physician in The Hague for a psychotic disorder and received a diagnosis of a schizophrenia spectrum disorder were eligible for the study. <u>Period:</u> between 1 October 2000 and 1 July 2005. <u>Case identification:</u> WHO 10-country study criteria (Jablensky et al., 1992). <u>Diagnosis Assignment-Classification:</u> DSM-IV: schizophrenia, schizophreniform disorder, schizoaffective disorder. <u>Ethnic definition:</u> census information; citizens' country of birth and that of their parents. <u>Population at risk:</u> for each patients two control subjects were recruited, matched for 5 years age group, sex and ethnicity (including generation). The first control group was recruited among the general ethnic minority population of The Hague. To minimize selection bias as a result of pathways to care, the controls were selected from immigrants who made contact with non-psychiatric secondary health care services. The second control group consisted of siblings of the patients, in order to (partially) control for genetic factors and to control implicitly for unmeasured shared socio-environmental confounding factors. Perceived discrimination were measured by International Comparative Study of Ethnocultural Youth (ICSEY). Odds ratios of schizophrenia for perceived discrimination, comparisons between cases and matched general-hospital controls were adjusted for marital status, unemployment, level of education, cultural distance, ethnic identity, social support, self-esteem, mastery, and cannabis use.	146 patients elegible, 100 interviewed (26F). Mean age: 26.6 Ethnicity: M: 29 T: 19 S: 32 O non Western: 20 Second generation: 36 Single marital status: 72	52% of the cases and 42% of both control groups reported experiences of discrimination, but this difference was not statistically significant. The other measures of perceived discrimination did not yield statistically significant differences between cases and controls either, except that cases reported more personal experiences of discrimination than general-hospital controls (OR per unit increase of the scale = 1.08 (95%CI_1.01–1.17)). After adjustment for unemployment, level of education, marital status, cultural distance, mastery, ethnic identity, self-esteem, social support, and cannabis use, there were no statistically significant differences in perceived discrimination between cases and controls. Perceived discrimination was positively correlated with cultural distance and negatively correlated with ethnic identity, mastery and self-esteem.
Selten et al., 2008 The Netherland, The Hague	Dutch and Moroccan-Dutch patients with non-affective psychotic disorder who had participated in the first-contact incidence study in The Hague (Veling et al., 2006) were asked for permission to interview a family member. Family member were interviewed about the presence of psychiatric disorders in first-degree relatives by means of the Family Interview for Genetic Studies	Same sample of Veling et al., 2008 29 Moroccan-Dutch 63 Dutch patients 508 first-degree relatives	The risks for NAPD in both parent groups were similar (age and sex-adjusted odds ratio 1.0; 95% CI: 0.3–3.8). However, among the siblings, the risk for NAPD was significantly higher for the Moroccan-Dutch than for the Dutch (sex-adjusted hazard ratio 4.5; 95% Confidence Interval: 1.5–14.0). This was due to a large number of cases among the brothers of the Moroccan-Dutch patients (N=14), not among their sisters (N=1).
Bresnahan et al., 2007 NY, US	<u>Cohort study</u> (Prenatal Determinants of Schizophrenia-PDS- Cohort) Subjects were offspring of women enrolled during pregnancy at	12 094 of the 19 044 cohort were followed-up	African Americans were about 3-fold more likely than whites to be diagnosed with schizophrenia [Rate Ratio (RR)=3.27; 95% confidence interval (CI): 1.71–6.27].

	Alameda County Kaiser Permanente Medical Care Plan clinics (1959–66) in the Child Health and Development Study. Period: live births were followed over 1981–97 Case Identification: Potential cases of schizophrenia and other schizophrenia spectrum disorders in the PDS cohort were identified through screening of computerized registries of treatments provided by or paid for by the Health Plan. Screening in the hospitalization registry identified PDS cohort members with any of several diagnoses that might be used for a non-affective or affective psychotic disorder (ICD-9 295, 296, 297, 298 and 299). Supplementary screening in outpatient and pharmacy registries was used to identify cohort members who may have been treated for psychosis without being hospitalized. Diagnosis Assignment-Classification: Assessments were conducted by clinicians with a minimum of a master's degree in a mental health related field using the Diagnostic Interview for Genetic Studies (DIGS) and trained to reliability. A DSM-IV diagnosis was assigned by consensus of three psychiatrists who reviewed the interview materials and charts. Ethnic definition Maternal ethnicity based on self-identification. The analysis is restricted to cohort members whose mothers identified as African American or white at intake Population at risk: Health Plan membership registry.	**Analytic sample:** African American 2128; White 4508 183 subjects were targeted for diagnostic assessment (144 hospital+ 39 outpatient/pharmacy registries). Face-to-face assessments were completed on 107 of the 183 targeted. • 32 cases of SSD (22 men and 10 women) among African Americans • 30 (20 men and 10 women) among whites	After adjusting for indicators of family SES at birth, the RR was about 2-fold (RR=1.92; 95% CI: 0.86–4.28). Using multiple imputation in the model including family SES indicators, the RR for race and schizophrenia was strengthened in comparison with the estimate obtained without imputation
Brown et al., 2007 NY, US	Nested case-control study (Prenatal Determinants of Schizophrenia-PDS- Cohort)	63 patients with schizophrenia and other spectrum disorders 122 controls belonged to the birth cohort matched to cases on date of birth, sex, length of time in the cohort, and availability of maternal serum samples	In the analysis that tested for a threshold effect of third trimester homocysteine on SSD risk, elevated maternal homocysteine was associated with a significant, greater than 2-fold increased risk of SSD (unadjusted OR, 2.39; 95% CI, 1.18-4.81; P=.02). Separate adjustment for maternal education, race, smoking, age, parity, and gestational age of the sera had no appreciable effects on the association between elevated maternal homocysteine and risk of schizophrenia (_10% change in _ coefficients) and thus did not meet our a priori criterion for confounding. Nonetheless, for further confirmation, we conducted a supplementary analysis that adjusted for maternal education and maternal race in the same model. The results were not appreciably changed in this model with only a 7.2% reduction in the _ coefficient (OR, 2.18; 95% CI, 0.98-4.86; P=.06).
Dean et al., 2007 Nottingham and South-East London, UK.	Aesop Study. Case-control study; all people aged 16-64 years presenting to mental health services with first episode of psychosis, residence within tightly defined catchment areas in Nottingham or South-East London. Period: 2 year 1997-1999. Case identification: Screening Schedule for Psychosis (Jablensky et al., 1992) Diagnosis Assignment-Classification: ICD-10 : schizophrenia (F20), manic psychosis (F30–31), depressive psychosis (F31–32), and 'Other Psychoses' (F10–19 and F21–29). Ethnic definition: principal source was self-ascription; when this was unavailable was used place of birth and place(s) of parental birth. Population at risk: Office of Population and Census Statistics Psychiatric Morbidity Survey.	245 patients 158 controls	Patients had a higher mean total Minor physical anomalies (MPA) score than healthy controls (n=158). This held true across each of the four ethnic groupings.
Morgan C, 2007 South-east London, UK	Aesop Study. Case-control - Incidence study; All first episode psychosis people, aged 16-64 years, presenting to	Same sample of Morgan 2008. 390 (172F) cases,	Cases were 3 times more likely to have experienced a **long term separation from one or both parents before the age of 16** (OR 3.36; 95%CI_2.41-4.7) and 3

Nottingham, UK	mental health services residence within tightly defined catchment areas in Nottingham or South-East London. Period : 6 year period (1997-2003). Case identification: Screening Schedule for Psychosis (Jablensky et al., 1992). Diagnosis Assignment-Classification: ICD-10 :F20-29; 30-33 Ethnic definition: self-ascription and standardized employing 11 categories used by UK census in 2001 (MRC Socio-demografic Schedule). Ethnic identification was assessed using Candi-1-A(Bhugra et al 1999). Population at risk: Office of Population and Census Statistics Psychiatric Morbidity Survey.	391 (230F) controls -263 non affective psychosis -127 affective psychosis Mean age: cases 30.5, controls 37.3. Ethnicity: WB 45.4% cases, 62.7% ctr. OW 6.9% cases, 9.5% ctr. BC 24.4% cases, 18.4% ctr. BA 10.5% cases, 5.1% ctr. A 5.4% cases, 1.8% ctr. O 7.4% cases, 2.5 % ctr. Generation: not specified	times more likely to have had **a parent die before the age of 16** (OR 3.19; 95%CI_1.62-6.26). The adjusted OR for separation from father was greater in the BC (4.73; 95%CI_1.82-12.32) than in the WB (2.23; 95%CI_1.20-4.16). Although there was no evidence that the effect of separation was stronger among BC there was evidence that all separations were more common in the BC, particularly separation from fathers only.
Cantor Graae E, 2007 Denmark	Cohort study: all person born in Denmark between 1954 and 1986 were followed during residence in Denmark from their 15th birthday or 1 April 1970, whichever came later, until onset of schizophrenia, death or 31 December 2001, whichever came first. Date of onset was defined as the first day of the first (in- or out-patient) contact with a diagnosis of schizophrenia. Period: 1970-2001. Case identification: Danish Psychiatric Central Register Diagnosis Assignment-Classification: ICD-8: code 295; or ICD-10: code F20. Parents and siblings were categorized hierarchically with a history of schizophrenia, schizophrenia like psychosis (ICD-8 codes 297,298.39, 301.83 or ICD-10 codes F21-F29) or other mental disorder (any ICD-8 or ICD-10 diagnosis) if they had been under out-patients care. Ethnic definition: census information: Danish Civil Registration System (CRS). Population at Risk : General Population (Danish Civil Registration system).	2 090 260 persons born in Denmark 10779 persons with schizophrenia: Natives: 9742 (90.4%) II Generation Immigrants by mother only: 436 (4%) II Generation Immigrant by father only: 332 (3.1%) II Generation Immigrants by both parents: 137 (1.3%) Person lacking information on parents country of birth: 132 (1.2%) Generation: only second generation	Adjusted RR of schizophrenia in second generation immigrants: one parent foreign born RR 1.93 (CI 1.79-2.08) both parents foreign born: RR 2.96 (CI 2.49-3.51) Not explained by urbanization at birth or during upbringing, parental characteristics pertaining to age, mental illness, geographic origin or residence abroad during a child's upbringing. Particular risks factors: -Urbanicity: Among second-generation immigrants by both parents, there was no evidence of a dose–response association between risk of schizophrenia and the degree of urbanization. -Family residence abroad at the child's 15th birthday A family member living abroad (child, mother, father or the entire family) versus the entire family living in Denmark at the child's 15th birthday increased the risk of developing schizophrenia (p<0.0001). -Parental region of origin is a more important effect than the developmental level of the country (Greenland)
Kirkbride JB, 2007 South-east.London, UK	Using data from AESOP study (case-control) .All cases of schizophrenia and other non affective psychoses aged 16-64 years across 33 wards in South East London Period: 2 year period, 1997-1999. Case identification: initial inclusion criteria were based upon those used in the WHO 10-country study (Jablensky et al., 1992); subjects who passed the screen underwent the SCAN and a modified Personal Psychiatric History Shedule. Diagnosis Assignment-Classification: ICD-10: F20; 21-29 Ethnic definition: ascribed using self-ascription, place of birth, and parental place of birth, rated independently by three researchers. Population at risk: Office of Population and Census Statistics Psychiatric Morbidity Survey.	218 (98F) cases -148 Schizophrenia (F20) -70 Other non affective psychoses(F21-29) Ethnicity: W: 55 (25%) BME: 163 (75%) Age: < 30: 50% >30: 50% Generation: not specified	*Individual level socio-environmental risk factors for schizophrenia:* BC: IRR 6.42 (95%CI_4.11-10.04) BA: IRR 3.93 (95%CI_2.39-6.46) Mixed ethnicity: IRR 2.57 (95%CI_1.07-6.16) WO: IRR 2.04 (95%CI_1.14-3.67) O: IRR 2.57 (95%CI_1.07-6.15) *Individual level socio-environmental risk factors for non-affective psychosis:* BC: IRR 4.78 (95%CI_2.67-8.5) BA: IRR 2.39 (95%CI_1.2-4.76) Mixed ethnicity: IRR 0.58 (95%CI_0.08-4.33)# WO: IRR 0.69 (95%CI_0.24-2.0)# O: IRR 0.58 (95%CI_0.08-4.33)# **Voter turnout and ethnic fragmentation** were significantly associated with schizophrenia. A 1% increase in voter turnout was associated with reduction in the

			incidence schizophrenia of 5% (IRR0.95; 95%CI_0.92-0.99). Similarly, as wards became less ethnically fragmented, the incidence of schizophrenia fell (IRR 0.95; 95%CI_0.92-0.99). The risk of schizophrenia for BME individuals was highest in the third of wards with the smallest proportion of BME residents: Lowest third IRR 6.50 (95CI_3.00-14.06) Middle third IRR 2.13 (95CI_1.17-3.88) Upper third IRR 3.81 (95CI_1.86-7.79) *Individual level socio-environmental risk factors for other non affective psychosis:* BC 4.96 (95CI_2.82-8.72) BA 2.5 (95%CI_1.27-4.91) Increased voter turnout associated with a lower incidence of other non affective psychoses (IRR 0.93; 95%CI_0.88-0.98). Ethnic fragmentation and deprivation were significantly associated with other non affective psychosis.
Veling W, 2007 The Hague, The Netherland	All first episode psychosis, aged 15-54, who made a first contact with a physician (general practitioner, psychiatrist, psychiatry resident) in the Hague Period: from Apr 1997 to Apr 1999 and Oct 2000 to Oct 2005. Case identification: WHO 10-country study criteria (Jablensky et al., 1992). CASH, IRAOS. Diagnosis Assignment-Classification: 2 psychiatrist made a consensus DSM-IV diagnosis : schizophrenia, schizophreniform disorder and schizoaffective disorder. Ethnic definition: census information; citizens' country of birth and that of their parents. Population at risk: municipal population register.	Same sample in Veling 2011, 2008a, 2007 and 2006. 678 cases identified, 497 interviewed 618 cases (182F): 273 immigrants 119 II gen. citizens 226 D citizen Mean age: 27.5 years Ethnicity: Dutch: 226 (36.56%*) S: -immigrant: 57 (9.22%*) -II gen. citizen:37 (5.98%*) N.A.: -immigrant: 17 (2.75%*) -II gen. citizen: 4 (0.64%*) T: -immigrant: 37 (5.98%*) -II gen. citizen:18 (2.91%*) M: -immigrant: 68 (11%*) -II gen. citizen: 23(3.72%*) O non W: -immigrant: 72 (11.65%*) -II gen. citizen: 25 (4.04%*) W: -immigrant: 22 (3.55%*) -II gen. citizen: 12 (2%*)	Incidence of schizophrenic disorders 33/100.000 **Across ethnic minorities groups the incidence of schizophrenic disorders increased with degree of perceived discrimination** IRRs EM 4.00 (95%CI_3.00-5.35), 1.99 (95%CI_1.58-2-51), 1.20 (95%CI_0.79-1.84) for high, medium, low and very low degree of discrimination, respectively. Further adjustment for socio-economic level of the neighbourhood slightly attenuated the effects of discrimination, particularly in the groups exposed to the most discrimination. IRR Adjusted for age and gender / IRR Adjusted for age, gender and socio-economic level of neighbourhood High Morocco: 4.00 (95%CI_3.0-5.35) / 3.52 (95%CI_2.56-4.83) Medium Netherlands Antilles: 1.64 (95%CI_0.93-2.9)# / 1.54 (95%CI_0.87-2.74)# Surinam: 2.21 (95%CI_1.66-2.94) / 2.05 (95%CI_1.52-2.77) Other non-western countries: 1.87 (95%CI_1.39-2.51) / 1.73 (95%CI_1.28-2.35) Low Turkey: 1.58 (95%CI_1.10-2.27) / 1.41 (95%CI_0.96-2.07)# Very low Western countries: 1.2 (95%CI_0.79-1.84)# / 1.17 (95%CI_0.76-1.81)# Native Dutch: 1 / 1
Veling W, 2006 The Hague, The Netherland	All first episode psychosis, aged 15-54, who made a first contact with a physician (general practitioner, psychiatrist, psychiatry resident) in the Hague	Were used partly the same sample in Veling 2011, 2008a, 2007 and 2006.	Adjusted IRR (age and gender) for schizophrenic disorder in ethnic groups in the Hague: *First generation:*

	Period: from Apr 1997 to Apr 1999 and Oct 2000 to Oct 2002 Case identification: WHO 10-country study criteria (Jablensky et al., 1992). Diagnosis Assignment-Classification: DSM-IV: : schizophrenia, schizophreniform disorder and schizoaffective disorder. Ethnic definition: census information; citizens' country of birth and that of their parents. For the first period psychiatrists who made the DSM-IV diagnosis were blind for the ethnicity. Population at risk: municipal population register.	Total cases 308 (91F) First generation cases (immigrants, total): 102* (28F) Ethnicity: M: 25 (24.5%)* S: 52 (27.5%)* Na: 5 (A. 4.9%)* T: 11 (10.8%)* O non Western: 26 (25.5%)* Western or Westernised: 7(6.8%)* Native Duch cases: 79* (24F) Second generation cases (immigrants, total): 48* (15F) Ethnicity: M: 10 (20.9%)* S: 15 (31.3%)* Na: 1 (2%)* T: 6 (12.5%)* O non-Western: 10 (20.8%)* Western orWesternised:6(12.5%)* Native Dutch: 79* (24F)	-Immigrants, total 2.3 (95%CI_1.7-3) -Moroccans 4 (95%CI_2.5-6.3) -Surinamese 2.6 (95%CI_1.7-4) -Others, non Western 2.2 (95%CI_1.4-3.5) *Second generation:* -Immigrants, total 2.5 (95%CI_1.7-3.7) -Moroccans 5.8 (95%CI_2.9-11.4) -Surinamese 2.9 (95%CI_1.6-5) -Turks 2.3 (95%CI_1-5.4) -Others, non Western 3.5 (95%CI_1.8-6.8) The higher IRR found was particularly relevant for **Moroccans men** both for first (5.2 [95%CI_3.2-8.4]) and for second generation(6.8 [95%CI_3.3-14.1)]. And particular high IRR was found in Surinamese women of first (3.6 [95%CI_1.8-7.0)] and second generation (3.9 [95%CI_1.4-10.6]).
Kirkbride JB, 2006 South-east London, Notthingam, Bristol,UK	AESOP study (case-control). Everyone between 16 and 64 who made contact with mental health services because of a first episode of any probable psychosis, non psychotic mania or bipolar disorder in South East London, Nottingham and Bristol. Period: from Sep 1997 to Aug 1999 and the first nine months of this period in Bristol. Case identification: WHO-study criteria Diagnosis Assignment-Classification: -Affective psychoses DSM-IV : 296.X4, 296.4,296.89 -Non affective psycoses DsmIV : 295.XX, 297.XX, 298.8, 299.9 -Schizofrenia DSM IV : 295.XX ; -Substance Induced Psychosis DSM IV 291.3,291.5.,292.11., 292.12 Ethnic definition: ascribed using self-ascription, place of birth and parental place of birth. Population at risk: Office of Population and Census Statistics Psychiatric Morbidity Survey.	568 total cases Men: 333 (59%); mean age: 29.6. Women: 235 (41%); mean age: 32.6. Ethnicity: W: 304 (53.5%) BME: 264 (46.5%) Generation. not specified.	IRR for psychoses in BME group vs WB: All psychoses: 2.9 (95%CI_2.4-3.5) Non Affective Psychosis: 3 (95%CI_2.4-3.7) Schizophrenia: 3.6 (95%CI_2.7-4.9) Affective Psychosis: 3.2 (95%CI_2.3-4.6)
Morgan C, 2006 South-east London, Notthingam, Bristol,UK	Aesop Study. Case-control - Incidence study; All first episode psychosis people, aged 16-64 years, presenting to mental health services residence within tightly defined catchment areas in Nottingham or South-East London. Period : 3 year period Period: (1997-2000) Case identification: Screening Schedule for Psychosis (Jablensky et	1004 subject: 592 cases and 412 controls. Mean age: -London: cases 31±10.5, ctr. 36.1±11.3 -Nottingham: cases 30.3±11.2, ctr. 38.4±13.4	Incidence of all psychosis is significantly higher in the **African Caribbean** population across all three centers compared with the baseline White British population IRR African Caribbean compared with White British 6.7 (95%CI_5.4-8.3). Narrowing defined schizophrenia IRR 9.1 (95%CI_6.6-12.6). Manic psychosis IRR 8 (95%CI_4.3-14.8).

	al., 1992). Diagnosis Assignment-Classification: ICD-10 :F20-29; 30-33 Ethnic definition: self-ascription and standardized employing 11 categories used by UK census in 2001 (MRC Socio-demografic Schedule). Population at risk: Office of Population and Census Statistics Psychiatric Morbidity Survey.	-Bristol: cases 30.7±10.8, ctr. 31.5±9.4 Male: -London: cases 186 (56.7%), ctr. 67 (36.6%) -Nottingham: cases 122 (59.5%), ctr. 95 (45.7%) -Bristol: cases 39 (68.4%), ctr. 9 (42.9%) Ethnicity: WB: -London: cases 78(23.6%), ctr. 76 (41.5%) -Nottingham: cases 151 (73.7%), ctr. 164 (78.9%) -Bristol: cases 37 (64.9%), Ctr. 19 (90.5%) AC: -London: cases 126 (38.2%), ctr. 51 (27.9%) -Nottingham: cases 27 (13.2%), ctr. 23 (11.1%) -Bristol: cases 10 (17.5%), ctr. 1 (4.8%) BA: -London: cases 66 (20%), ctr. 21 (11.5%) -Nottingham: cases 3 (1.5%), ctr. 1 (0.5%) -Bristol: cases 5 (8.8%), Ctr. 0 (0%)	Incidence of all psychosis was also markedly elevated in the **Black African** population IRR Black African 4.1 (95%CI_3.2-5.3), Narrowing schizophrenia IRR 5.8 (95%CI_3.9-8.4) manic psychosis IRR 6.2 (95%CI_3.1-12.1). The incidence rates for all psychosis were also raised for all other ethnic groups (**other White, Asian and Mixed**) compared with the WB population, albeit much more modestly IRR ranged from 1.5 to 2.7). BA and AC more likely to be compulsory admitted, to access the services via police, less likely to access the psychiatric services via general practitioners. Not found ethnic differences in DUP.
Fearon P, 2006 South-east London, Notthingam, Bristol,UK	Aesop Study. Case-control study; all people aged 16-64 years presenting to mental health services with first episode of psychosis, residence within tightly defined catchment areas in Nottingham or South-East London over a 2 year. Period: 1997-1999 and 9 months period in Bristol. Case identification: Screening Schedule for Psychosis (Jablensky et al., 1992) Diagnosis Assignment-Classification: ICD-10 : schizophrenia (F20), manic psychosis (F30–31), depressive psychosis (F31–32), and 'Other Psychoses' (F10–19 and F21–29). Ethnic definition: principal source was self-ascription; when this was unavailable was used place of birth and place(s) of parental birth. Population at risk: Office of Population and Census Statistics Psychiatric Morbidity Survey.	568 cases London: 308 cases Nottingham: 203 cases Bristol: 57cases (only 9 month)	Remarkably high IRRs for psychosis and schizophrenia in **African Caribbeans and Black Africans**. IRRs in other ethnic minority groups were modestly increased. All Psychosis: (F20-33) -AC: IRR 6.7 (95%CI_5.4-8.3) -BA: IRR 4.1 (95%CI_3.2-5.3) -Asian: IRR 1.5 (95%CI_0.9-2.4)# -Other: IRR 2.6 (95%CI_1.7-3.9) -Mixed: IRR 2.7 (95%CI_1.8-4.2) -WO: IRR 1.6(95%CI_1.1-2.2) Manic psychosis: (F30-31) -AC: IRR 2.2 (95%CI_4.3-14.8) -BA: IRR 6.2 (95%CI_3.1-12.1) -Asian: IRR 2.7 (95%CI_0.9-7.6)# -Other: IRR 3.0 (95%CI_0.9-10.0)# -Mixed: IRR 6.2 (95%CI_2.6-15.0) Narrow Schizophrenia: (F20) -AC: IRR 9.1 (95%CI_6.6-12.6) -BA: IRR 5.8 (95%CI_3.9-8.4) -Asian: IRR 1.4 (95%CI_0.7-3.1)# -Other: IRR 3.5 (95%CI_1.9-6.5) -Mixed: IRR 2.6 (95%CI_1.2-5.3) -White Other: IRR 2.5(95%CI_1.6-3.9) Depressive psychosis: (F32-33) -AC: IRR 3.1 (95%CI_1.5-6.1) -BA: IRR 2.1 (95%CI_0.9-5.0)# -Asian: IRR 3.0 (95%CI_1.3-7.1) -Other: IRR 5.6 (95%CI_2.5-12.4) -Mixed: IRR 4.0 (95%CI_1.6-10.2)

			-WO: IRR 1.7 (95%CI_0.6-4.3)# -WO: IRR 1.3 (95%CI_0.5-3.2)# Other psychosis: (F10-29) -AC: IRR 5.5 (95%CI_3.8-8.0) -BA: IRR 2.7 (95%CI_1.6-4.5) -Asian: IRR 0.6 (95%CI_0.2-1.9)# -Other: IRR 0.3 (95%CI_0.1-2.2)# -Mixed: IRR 1.3 (95%CI_0.5-3.5)# -WO: IRR 0.8 (95%CI_0.4-1.7)#
Cantor-Graae E, 2005 Sweden, Malmo	All first episode psychosis, aged of - 54 years who had contact with psychiatric (self referral to out-patient sector clinics or to the emergency psychiatric treatment facility at Malmo¨'s sole general hospital; referral to psychiatric services by physicians at other clinics, social services, police authorities, schools, or family members). Period: 1 January 1999 - 31 December 2001. Diagnosis Assignment-Classification: DSM IV: schizophrenia, schizoaffective disorder, schizophreniform disorder, or for other non-affective psychosis (i.e. 297.1, 298.8, 298.9). Ethnic definition: census information: Malmo Municipal Person Register	150 cases (34 of whom with Schizophrenic disorder) Swedish n. 56 (37,3%*) Immigrants: First generation: 79 (52,7%*) Second generation: 15 (10%*) Mean age at first contact: I generation: 35.0 II generation: 23.8 Sw: 31.7 Male: 78 (52%*); mean age: 30.6 Female:72(48%*); mean age: 34.9	Relative risks for these disorders were not significantly increased in second-generation immigrants. Natives: Psychotic disorder 1; Schizophrenic disorder 1 I generation: 2.9 (95%CI_2.0-4.0); 4.0 (95%CI_1.8-8.6) IIgeneration: 1.4 (95%CI_0.8-2.4)#; 2.0 (95%CI_0.7-5.9)# The highest risks of developing psychotic disorder compared to Swedes were found in First-generation immigrants with "**black**" **skin color** (RR 5.8 (95%CI_2.8-13.4)), medium in those with "neither black nor white" skin color (RR 2.6 (95%CI_2.0–4.2)) and slightly low in those immigrants with white skin (RR 2.6 (95%CI_1.64.2)). Adjusted relative risk among first generation immigrants from both developed and from developing countries versus natives Swedes were 2.2 (95%CI_1.3-3.6) and 3.3 (95%CI _2.3–4.8) respectively.. The increased risk obtained especially in immigrant groups having relatively disadvantaged status in Sweden suggests that psychosocial factors may contribute to the development of psychotic disorder.
Mallet R, 2004 Camberwell (South London) and Ealing (West London), UK.	Case-control study All first episode psychosis aged 18- 64, resident for at least 6 months in the catchment area of Camberwell (South London) and Ealing (West London), Period: 1991 and 1993 Case identification: psychotic symptoms (Present State Examination) Diagnosis Assignment-Classification: Catego Program (Wing et al., 1974) Ethnic definition: self-ascription using the categories devised for the 1991 Census. Population at risk: Electoral wards in Camberwell and Ealing	Same sample of Mallet R. 2002 Data on expectations and achievement were collected on 83 patients and their matched controls. 83 Patients(35%F): 33 AC(87% of the past sample) 32 WB (84% of the past sample) 18 In(75% of the past sample) Mean age cases/controls: AC 25.5/27.2 WB 28.5/31.6 In 37.6/39.4 Generation: not specified	The AC cases differed from the other minority ethnic group and from their controls by being more likely to be **living alone** ($p < :0.013$). W and AC patients had significantly higher levels of **unemployment** than their peer controls ($p < :001$), the AC cases were more likely to be unemployed than those of the other two ethnic groups ($p < :0.003$). Cases of all three ethnic groups were significantly less likely to have **advanced beyond secondary education** than their matched controls. The gap between achievement and expectations did not appear to cause high disappointment levels in any group, and in fact only in the domain of housing did the AC patients assess their current achievement as being significantly lower than that of their matched controls($p<: 0.001$). Quality of the current accommodation weren't assessed by any standardised measure, so we cannot say whether their perceptions represent an accurate appraisal. Only in the subjects showed differences in employment domain, the patients seeing themselves as worse off now ($p<: 0.001$) and in the future ($p<: 0.001$) than the controls. The W patients view themselves as of significantly lower social standing currently than their controls ($p<: 0.001$), and the Indian patients showed a trend in the same direction ($p<: 0.01$). This difference was not shown by the African-Caribbean patients.
Cantor Graae, 2003 Denmark	Retrospective Cohort. Period/Study population: born between 1 January 1954 - 31 December	Were used partly the same cohort of Cantor-Graae 2007.	**Foreign birth :** RR 2.45 (95%CI_2.25-2.67) Significant differences among **regions of birth** ($p<0.001$)

	1983 who were resident in Denmark by their fifteenth birthday Period: 1970-1998. Case Identification: Danish Psychiatric Central Register (admission to inpatients and outpatients facilities) Diagnosis assignment: schizophrenia (ICD-8 code 295 and ICD-10 code F20) Ethnic definition: census information (from Danish Civil Registration System); place of birth and place(s) of parental birth. Statistical information: Danish Civil Registration System	10.244 persons developed schizophrenia during the 32.6million person follow-up Gender: Male 6748 (65.9%*) Female: 3496 (34.1%*) Age: 15-19: 1600 (15.6%*) 20-24: 3346 (32.7%*) 25-29: 2517 (24.6%*) 30+: 2781(27.1%*) Ethnicity: Unknown: 26 (0.3%*) Europe: 178 (1.7%*) Scandinavia: 106 (1%*) Asia: 74 (0.7%*) Middle Est: 29 (0.3%*) Australia: 11(0.1%*) Africa: 41(0.4%*) North America: 36 (0.3%*) South America: 15 (0.1%*) Greenland: 81 (0.8%*) Denmark, other: 537 (5.6%*) Denmark, II gen immigrants: 426 (4%*) Denmark, Danish background: 8684 (84.7%*)	[interestingly no indication that foreign born possible adoptees are at increased risk compared with foreign-born individuals from the same countries] Increased risk among **second generation immigrants** RR 2.09 (95%CI_1.85-2.35) The effect of IIgen immigrant status was confounded only slightly when adjusting for history of psychiatric disorder in parent RR 1.42 (95%CI_1.2-1.68) Age at first residence and n° of years lived in Denmark had no effect on RR Age of onset similar in native and I and II G **Individual with Danish background (born in Denmark with mother born in Denmark) and with a history of foreign residence prior to their fifteenth had an increased RR compared with those born in Danish background but no migration history RR 1.6 (95%CI_1.25-2.05)**
Mallett R, 2002 Camberwell (South London) and Ealing (West London), UK.	Case-control study All first onset psychosis, between ages 18 and 64, resident for at least 6 months in the catchment area of Camberwell (South London) and Ealing (West London), Period: 1991 and 1993 Case identification: psychotic symptoms (Present State Examination) Diagnosis Assignment-Classification: Catego Program (Wing et al., 1974) Ethnic definition: self-ascription using the categories devised for the 1991 Census. Population at risk: Electoral wards in Camberwell and Ealing	100 Patients: AC: 38 WB: 38 A : 24 100 matched controls Mean age cases: AC: 26.3 WB: 30.7 A: 38.1 2nd generation cases: AC: 27/38 W: 34/38 A: 4/24 2nd generation controls: AC: 34/38 WB: 28/38	**Unemployment** significantly contributed to the excess of AC cases OR 15.03 (95%CI_1.95-114.80) **Living alone** was not associated with caseness for any ethnic group. Separation was not associated with schizophrenia when all cases and controls were compared, but the association was significant for the AC patients compared to both their own controls and to the patients from other ethnic groups OR 5 (95%CI_1.09-22.82).

		A: 2/24	
Boydell J, 2001 South London, UK	Retrospective All first episode psychosis, over 16 years, who had first contact with psychiatric services. Period: 1988-97. Case identification: hospital computer records case notes from psychiatric services and case notes of all patients from area who had psychiatric hospital records to identify people who made contact with service but were not admitted to hospital. Diagnosis Assignment-Classification: ICD 9: 295,295.6, 296, 296.2, 296.4, 297, 298, 292.1; ICD 10: F20, 25, 22, 30, 31.3, 31.2, 31.6, 28, 29, 12.5, 16.6, 19.5, 16.75, 19.75. Ethnic definition: self-ascription according to categories used by the Office of Population Census and Surveys. For patients who did not have statements of self assigned ethnicity was used patient's and parents' place of birth and any description of color. Population at risk: Office of Population Census and Surveys	222* (96F) Mean age: 35.4 Ethnicity NW: 126 (57%*) I: 10 (4,5%*) NBW: 5 (2,25%*) Generation: not specified	Non white ethnic minorities IRR: 3.28 (95%CI_2.49-4.34). Incidence of schizophrenia in non-White ethnic minorities increased significantly as the proportion of such minorities in the local population fell. The incident rate ratio varied in a dose-response fashion in three groups divided according the ethnic proportion: -Highest third 2.38 (95%CI_1.49-3.79) where non-White ethnic minorities formed the largest proportion (28-57%), -Middle third 3.63 (95%CI_2.38-5.54) where non-White ethnic minorities formed the medium proportion (23-28%), -Lowest third 4.4 (95%CI_2.49-7.75) where non-White ethnic minorities formed the smallest proportion (8-22.8%).
Zolkowska K, 2001 Malmo, Sweden	Prospective All patients admitted to in any adult psychiatric in-patients or out-patients treatment unit in Malmo. Period: 1 April 1997 to 31 March 1998. A list was also generated of all SLP (schizophrenia-like psychoses) patients, who, because of psychotic symptoms, had their first-in-lifetime contact (whether primary or referred by another helping agency) with any of the out-patient sector clinics in Malmo during the period Period: 1 January 1998 to 31 December 1998. Case identification: In order to increase the likelihood of identifying all SLP cases, sector clinics supplied information on all patients age 18±64 who might fulfill the diagnostic criteria. Diagnosis Assignment-Classification: SLP (schizophrenia like psychosis) was defined: DSM IV: Schizophrenia (including 295.70), schizophreniform disorder, other non affective psychosis (297.1, 298.8, 298.9), affective disorder broadly defined (296.xx, 311.00, 300.40), bipolar disorder (296.4, 296.5, 296.6), major depressive disorder (296.2, 296.3). Ethnic definition: census information: Malmo Municipal Person Registry. Ethnicity for each patient was established by a research secretary without knowledge of the individual's diagnostic status. Population at risk: Malmo Municipal Person Registry	56 cases Natives: 34 (61%*) I generation immigr.: 22 (39%*) Mean age Natives: 32.1 I generation immigr.: 28.6 Ethnicity: Natives: 34 (61%*) Y and eastern Eu: 10 (18%*) Af: 3 (5%*) ME: 3(5%*) Other Nordic: 2 (3.6%*) A: 2 (3.6%*) South Am: 2 (3.6%*) 1162 (all psychiatric diagnosis),(897 natives, 265 immigrants) Schizophrenia Like Psychosis: 369 (natives: 250 (124f); immigrants: 119 (62f) Schizophrenia (narrow): 249 (natives: 177; immigrants: 72) Mean age: immigrants 44.7; natives 46.9 Etnicity (for SLP): Y, EE: 52 (44%)	The age- and sex-adjusted RR for first-onset SLP for immigrants based on background population rates was 1.88 (95%CI_1.10-3.22; *p*=0.02). Mean length of stay in Sweden prior to illness debut for first-onset SLP immigrants was 11.3 years (s.d.=7.2, range 2-30). Immigrants had significantly increased risk for admission for schizophrenia like psychosis (RR 1.42; 95%CI_1.14-1.77) but not for any other diagnostic categories, including admission or compulsory admission for any diagnosis. Relative risk for SLP admission was most markedly increased in immigrants from East Africa. **Background factors specifically associated with migration (e.g. extreme duress) did not appear to contribute strongly to SLP in immigrants.**

		Nordic Countries: 17 (14%) Af: 13 (11%) ME: 13 (11%) E: 11 (9%) A: 8 (7%) Am: 4 (3%) U: 1 (1%)	
Schaefer et al., 2000 NY, US	Cohort study (Prenatal Determinants of Schizophrenia-PDS- Cohort)	Because of missing data for prepregnant weight, the analyses reported in this article are based on 63 cases of schizophrenia and spectrum disorders (38 cases of schizophrenia) and 6,570 unaffected individuals	High prepregnant BMI was associated with almost three times the risk of schizophrenia and spectrum disorders in adult offspring compared with that of offspring born to women with average prepregnant BMI. The association was independent of the possible confounding effects of other maternal characteristics, including maternal age, race, education, parity, psychiatric complaints, and cigarette smoking. The association was not modified by gender of the offspring and it was not limited to schizophrenia and spectrum disorder cases with early age at first treatment.
Cantwell et al., 1999 Nottingham, UK	All first episode psychosis, aged 16-64, making first contact with the mental health services in Nottingham. Case ascertainment included all service contacts, in addition to first hospital admissions. Period: 1992-1994. Case identification: over-inclusive psychosis screen, SCAN, PPHS, SANS. Diagnosis Assignment-Classification: ICD 10: F20-29 (excluding F21, Schizotypal Disorder), F30-39. Ethnic definition: self-ascription using 1991 census' categories. Population at risk: 1991 census	Same sample of Harrison et al., 1997 168 cases	Drug misuse was associated with younger age of onset of psychosis, male gender and non-African-Caribbean ethnicity
Harrison G, 1997 Nottingham, UK	All first episode psychosis, aged 16-64, making first contact with the mental health services in Nottingham. Case ascertainment included all service contacts, in addition to first hospital admissions. Period: 1992-1994. Case identification: over-inclusive psychosis screen, SCAN, PPHS, SANS. Diagnosis Assignment-Classification: ICD 10: F20-29 (excluding F21, Schizotypal Disorder), F30-39. Ethnic definition: self-ascription using 1991 census' categories. Population at risk: 1991 census	168 cases Mean Age: 31 (AC: 31) Etnicity E: 124 (74%*) AC: 32 (19%*) -I gen. AC: 6 (19%*) -II gen. AC: 26 (81%*) Af: 3 (2%*) South A: 9 (5*%)	Subject born in the **Caribbean**, or who had one or both parents born in the Caribbean, had a greatly elevated risk for all psychotic disorders (RR 8.73; 95%CI_6.13-12.28) and for schizophrenia (RR 8.5; 95%CI_4.4-16.5). The sex ratio for all psychosis was 1.7:1 (**M**:F) in AC subjects compared with 1.3:1 (M:F) in the remaining population; there were few differences in mode of onset or in socio-demographic indices. There were no differences in reported substance use but **the AC group reported significantly less substance misuse according to ICD-10 criteria.**
Bhugra, 1997 London, UK	All first episode psychsosis, 18-64 years residing in 2 health districts in London who made contact with hospital or community services. Period: 1 April 1991-31 March 1993. Case identification: I psychosis screening, WHO; II Present State Examination (Wing et al., 1974) or Syndrome Check List (Wing et al. 1974). Diagnosis Assignment-Classification: CATEGO Program (Wing et al. 1974).	100 patients with schizophrenia W: 38 (12F) AC: 38 (10F) A: 24(13F) Second Generation 35	Incidence rate per 10000: W: 2.9; AC: 5.1; A: 3.7; Rate ratios EM to white AC: 1.7 (95%CI_1.1-2.8); A 1.3 (95%CI_0.8-2.1)# AC: A 1.4 (95%CI_0.8-2.3)#; A: W 1.28 (95%CI_0.8-2.1)# AC at higher risk in UK of developing FE schizophrenia ;AC men were at risk on

	Ethnic definition: self-ascription using the categories developed for 1991 census. Population at risk: 1991 census		all age(18-29/30-64), but in AC female only under 30; compared to white only Asian women older than 30 were at risk. **these findings suggest that factors involved in the etiology of schizophrenia operate differently over the life circle for the different ethnic groups** AC were more frequently unemployed; **unemployment** is a candidate factor to explain the excess of incidence of S in UK AC.
King, 1994 North London, UK	All first episode psychsosi, aged 16 to 54 years who were resident in the catchment area of St. Anna's Hospital and made contact with health services (in- and out-patients). Period: 1 July 1991 and 30 June 1992. Case Identification: Harrison et al. screening criteria Diagnosis Assignment-Classification: ICD-9 and DSM III (consensus discussion between clinical members and research team) . Ethnic definition: self-ascription using the categories developed for the 1991 census. Statistical information: 1991 census using figures for England supplied by the Office of Population Censuses and Surveys.	103 identified, 93 recruited. Mean age: 27.2 M; 31.9 F Ethnicity: White:39 -Br:18 (19.4%*) -I: 5 (5.4%*) -G or T Cipriot:7 (7.5%*) -Other Eu:9 (9.7%*) Black: 38 -AC: 19 (20.4%*) -Af: 14 (15%*) -Black other: 5 (5.4%*) Asian: 11 -In: 5 (5.4%*) -Pakistani: 3 (3.2%*) -Other A: 3 (3.2%*) Other: 5 (5.4%*) Generation: -54 cases born in UK -40 cases one or both parents born abroad -11both parents born in UK -3 parents' place of birth uncertain	Total age Standardized Annual Incidence of schizophrenia was 2.2/10000 (95%CI_1.5-2.9); 1.2/10000 in White(95%CI_0.6-19)# , 4.6/10000 in Black (95%CI_2.2-7.2), 6/10000 in Asian (95%CI_1.6-10.5), 3.9/10000 in Other (95%CI_0-9.2)#; Total age standardized annual incidence of non affective psychosis was: 3.6/10000 (95%CI_2.7-4.5); 2.0/10000 in White (95%CI_1.2-2.8), 8.1/10000 in Black (95%CI_5.3-12), 6.9/10000 in Asian (95%CI_2.1-11.6), 5.8 in Other (95%CI_0-12.3)# All ethnic minorities incidence rate 3.6 (95%CI_1.9-7.1); 3.7 (95%CI_2.2-6.2) for non affective psychosis. Not variation in DUP, type of onset (acute or insidious), and difference in compulsory admission between B and W; higher rate of W had been admitted at the ascertainment and more unusual psychotic syndrome in B. 85% cases were born abroad or had at least one parent who had been born abroad. Most white patients with schizophrenia were also first or second generation migrants.
Harrison G, 1988 Nottingham, UK	All first episode psychsosi,aged 15-54, of likely AC ethnic origin, including out-patients, in-patients and those presenting at the accident and emergency departments or on domiciliary visits, Period: September 1984- August 1986. Case identification: patients were screened for psychotic symptoms and regular checks were made upon acute admission wards(Present State Examination (PSE), Syndrome Checklist (Wing et al 1974)). Additional check with Nottingham Case Register. Diagnosis Assignment-Classification: 1-Schizophrenia certain: the main diagnosis is any of the schizophrenic categories except schizoaffective type (295.0-295.9, except 295.7), and no alternative diagnosis given; 2-Schizophrenia very likely: the main diagnosis is as for 1, but an alternative diagnosis is also given (any code); 3-Schizophrenia probable: the main diagnosis is schizoaffective	42 patients (36 became in-patients) ICD-9 for "certainty of schizophrenia": Certain:16 (38%); Very likely: 12 (29%); Probable: 3 (7%); Possible: 5 (12%); No schizophrenia: 6 (14%) of which: 2 Unspecified psychosis (295.9); Restrictive ICD-9 diagnoses (certain and very likely	Mean annual incidence rates for schizophrenia per 10 000 population: ICD-9: Caribbean General population 16-29: 29.1 2.2 30-44: 19.7 1.6 DSM-III: Caribbean General population 16-29: 17.5 0.98 30-44: 16.9 1.0 Rates among AC are twelve to thirteen times higher than those in the general population for the age group 16-29 and 30-44. mean annual incidence rates are found to be 36.4 per 10 000 for the age 16-29 (18

	psychosis (295.7) or a paranoid psychosis (including psychogenic psychosis) (i.e. 297.0-297.9, 298.3, 298.4); 4-Schizophrenia possible: the alternative diagnosis is a schizophrenic or paranoid category as in 1-3, but the main diagnosis is not; 5-No schizophrenia: neither main nor alternative diagnosis are any of the schizophrenic or paranoid categories; Diagnoses were also made using Research Diagnostic Criteria (RDC) (Spitzer et al. 1975) and DSM-III criteria Ethnic definition: "likely Afro-Caribbean ethnic origin" includes all those having physical characteristics of this ethnic group and who were likely to be so regarded by the local community. Statistical information: 1981 Census "Head of Housholds" population figures, without the GLC correction factor (Greater London Council) and with no attempt to compensate for changes in age bands since 1981.	categories): 28 (12F) Aged 16-29: 14(6F); Aged 30-44: 2(5F); Aged 45-54: 0(1F); Generation: of 28 patients meeting restrictive ICD-9 criteria 18 were born in the UK (17 fell into age range 16-29)	times the rate in the general population). The majority of patients (93%) diagnosed as having restrictive ICD-9 schizophrenia were therefore either born in UK, or came to this country as children. 64% of AC patients had onset of one week or less compared with only 22% of the general population group falling outside "restrictive ICD-9schizophrenia" coding, but for "restrictive schizophrenia" diagnoses, the mode of onset was very similar.
Bebbington, 1981 South London, UK	A-Register Study: All first episode psychosis, aged 15-64 in Camberwell Period:1970-1978. Case-identification: Camberwell register. (rates of new episodes and admission for native-born, Irish born and West Indian born) Diagnosis Assignment-Classification: ICD 1978: schizophrenia, B-Population Survey: prevalence study with random sample of 800 subject aged 18-64 in the former borough of Camberwell. Period: 1980 Case-identification: Present State Examination (PSE) Diagnosis Assignment-Classification: ICD 1978: any mental pathology. Ethnic definition: not specified. Statistical information: in 1971 a total census by sex and age was taken and a 10% sample of the London Borough of Southwark was used for a fuller enquiry which gave figures by age, sex and country of origin for the Camberwell area, which constitutes the southern two-thirds of the Bourough of Southwark. This assumes that immigrants are uniformly distributed throughout Southwark.	Register Study: no demographic data for cases. Camberwell general pop. in1971: UK:78196 (40149F) AC: 6564 (3316F) I:5093 (2617F) A: 892 Population Survey: sample of 800 subjects: - 611 Br -69 WI -32 I -plus smaller group from other country. Mean age: - Generation: not specified.	The most striking finding in the study were the high rates of schizophrenia in **west Indians and especially in females.** Mean rate per 100000 of new episode of schizophrenia: UK: Male 117.8 Female 101.6 AC: Male 331.8 Female 483.8 I: Male 82.5 Female 232.6 Irish males show half, and Irish females over twice, the rates of schizophrenia in the native-born. From the population survey study emerged interesting data about the social class of people living in Camberwell: AC were significantly more likely ($p<0.02$) to be **working class**. Only 36% of AC as opposed to 52% of native British were middle class. However, 61% of the AC males were skilled in manual occupations, compared with only 42% of native British, and relatively fewer of them were in the lowest two occupational classes. The same percentages of AC and British men were in employment. Ac women differed significantly from those born in Britain in that two-third were in full-time employment compared with less than half the British. Characteristically they were employed in more menial jobs, equivalent to the lowest socio-economic group.
Rwegellera, 1977 South London, UK	All West Africans and West Indian patients, with an address in the former London borough of Camberwell, who made a psychiatric contact (in- and out patients) for the first time Period: between 1 January 1965 and 31 December 1968. Case Identification: Camberwell Psychiatric Case Register Diagnosis Assignment-Classification: Schneider 1959: Schizophrenia, paranoid schizophrenia, paranoid state, endogenous depression, mania/	Camberwell general pop. in1966: 717 West Af 6800 AC Ethnicity of cases: UK: -Schizophrenia: 66 -Affective psychosis: 273 -Paranoid states: ---	The inception rates of schizophrenia, affective illness and paranoid states were significantly higher among **West African men** than woman. The inception rate of schizophrenia for those aged 15-24 and 25-44 is significantly higher among WA than B. Inception rates per 1 000 of the population at risk per annum: Schizophrenia: West Af 4.18, AC 0.92, UK 0.12 Affective illness: West Af 4.18, AC 0.92, UK 0.51 Paranoid states: West Af 1.05, AC 0.40, UK ---

	hypomania, Schizo-affective psychosis, reactive depression, anxiety Ethnic definition: not specified. Population at risk: Office of Population Censuses in Camberwell (the 1966 10% sample census).	West Af: -Schizophrenia: 12 -Affective psychosis: 12 -Paranoid states: 4 AC: -Schizophrenia: 25 -Affective psychosis: 26 -Paranoid states: 12 Mean age:- Generation: not specified.	For each diagnostic category the inception rate is significantly higher among West Africans than British living in Camberwell. Thus the inception rate of schizophrenia among WAf is more than 33 times that among B. Inception rate of schizophrenia and paranoid state were each significantly higher among AC men than woman.. The inception rates of schizophrenia decreased with age. For each age interval West Indians had higher inception rate of each of the main 4 diagnostic categories than the British (schizophrenia, paranoid state, affective illness, reactive depression). For those aged 15-24 and 25-44 years the inception rate of schizophrenia was significantly higher among West Africans than among AC.

Hospital setting-Psychiatric Admission : 9			
Werbeloff N, 2012 Israel	All people resident in Israel, aged 15 or over, with a first hospitalization for schizophrenia. Period: 1978–1992. Case-identification: case registry. Diagnosis Assignment-Classification: ICD 9 (not specified which specific code was used). Ethnic definition: categories utilized by Israeli Central bureau of statistics. Population at risk data from CBS on country of birth were the denominator. Incidence was calculated with cross-tabulations of the number of new cases by: country, sex, and year of first psychiatric hospitalization.	Same sample of Rabinowitz J, 2002Israel 10892 cases Ethnicity Is: 8557 (78.6%*) 1st generation immigr.:2335(21.4%*) Far East 65(27F) Caribbean and South America 59(25F) Middle East 1320(632F) Eastern Europe 629(277F) USA, Commonwealth and South Pacific Ocean 68(25F) Africa 25(7F) Central and Western Europe 169(86F)	**Immigrants** were at a higher risk of schizophrenia as compared to native-born Israelis (RR = 1.6, 95%CI_1.53-1.68). On aggregate, immigration-related risk was higher among female (RR = 1.91, 95% CI _1.78-2.04) than male (RR = 1.39, 95%CI_1.3-1.47) Across migrant nation groupings, except for men from the USA, Commonwealth and South Pacific Ocean and Africa, **women** were at greater risk than men. -Far East males RR 2.36 (95%CI_1.72-3.24); females RR 2.57 (95%CI_1.91-3.1); -Caribbean and South America males RR 1.83 (95%CI_1.3-2.55); females RR 2.13 (95%CI_1.51-2.51); -Middle East males RR 1.42(95%CI_1.31-1.53); females RR 2.09 (95%CI_1.92-2.27); -Eastern Europe males RR 1.81 (95%CI_1.6-2.05) females RR 1.62 (95%CI_1.5-1.76) -USA, Commonwealth and South Pacific Ocean males RR 1.6(95%CI_1.18-2.15) females RR 1.44 (95%CI_0.98-2.14) -Africa males RR 1.83 (95%CI_1.16-2.89) females RR 1.21 (95%CI_0.59-2.49)# -Central and Western Europe males RR 0.83(95%CI_0.67-1.03)# females RR 1.32 (95%CI_1.07-1.64) Were examined annual trends in the association between immigration and schizophrenia by disaggregating by year, sex, and migrant's nation. Results showed that there was generally a linear trend of reduced relative risk over time. **People who migrated prior to the age of 15** (n = 2,335) were at a greater risk of schizophrenia (n = 8,557; RR = 1.6, 95%CI_1.53; 1.68), particularly those from Far Eastern (RR = 2.43, 95% CI_1.91; 3.1) and Caribbean and South American (RR = 1.94, 95% CI_1.51; 2.51) countries.
Corcoran C, 2009 Israel	This study relies on a population-based research cohort known as the Jerusalem Perinatal Study. In 1964–1976, all births were recorded for mothers resident in a defined geographic area of Jerusalem. Demographic data, including	88 829(42 957F) Parents' ethnicity: Mother/Father	There was no change in risk of schizophrenia for offspring of immigrants, including those who had only 1 immigrant parent and those who had 2 immigrant parents. There was no association between length of time in Israel since immigration and risk of schizophrenia in the offspring.

	the parents' countries of birth, were copied from the birth notification. Period: all people born in 1964-1976 followed until December 31 1997. Case identification: Israel's National Psychiatric Registry. Diagnosis Assignment-Classification: ICD-10: F20–F29 (schizophrenia, schizotypal disorder, delusional disorders, non affective psychoses, and schizoaffective disorders). Ethnic definition: parents' counties of birth. Israel, other West Asia (including Iraq, Iran, Afghanistan, Turkey, Syria, Lebanon, and Yemen), North Africa (mainly Morocco), or Europe (mainly Poland, Union of Soviet Socialist Republic, and Eastern Europe), the latter including the Americas and other industrially developed countries, hereafter "Europe, etc." Parents born before 1948 in the British-controlled region that was to become the state of Israel were considered to have been born in Israel. Population at risk: Jerusalem. Demographic data	Is/ Is: 27 755 (192cases) Is/ O West Asia: 4 456 (29cases) Is/ North Af: 2 630 (15cases) Is/ Eu, etc.: 5 621(41cases) O West Asia/ Is: 3 259(28cases) O West A/ O West A:11 809 (88cases) O West A/ North Af: 848 (5cases) O West A /Eu, etc.: 548 (7cases) North Af/ Is: 2 478 (24cases) North Af /O West A: 1380(6cases) North Af /North Af: 13150 (110cases) North Af /Eu, etc.: 810(8cases) Eu, etc./ Is: 5187 (29cases) Eu, etc./ O West A: 606 (3cases) Eu, etc./ North Af: 729 (3cases) Eu, etc./ Eu, etc.: 7563 (49cases)	Adjusted Relative risk: (no result is statistically significant) Mother/Father Is/ Is: 1 Is/ O West Asia: 0.9 (95%CI_0.6-1.3/p=0.6)# Is/ North Af: 0.9 (95%CI_0.5-1.5/p=0.7)# Is/ Eu, etc.: 1(95%CI_0.7-1.4/p=1)# O West Asia/ Is: 1.1 (95%CI_0.7-1.6/p=0.8) # O West A/ O West A: 0.8 (95%CI_0.6-1.1/p=0.2)# O West A/ North Af: 0.7 (95%CI_0.3-1.8/p=0.5)# O West A /Eu, etc.: 1.4 (95%CI_0.7-3.0/p=0.4)# North Af/ Is: 1.3 (95%CI_0.9-2.0/p=0.2) # North Af /O West A: 0.6 (95%CI_0.3-1.3/p=0.2)# North Af /North Af: 1 (95%CI_0.7-1.2/0p=0.8)# North Af /Eu, etc.: 1.2 (95%CI_0.6-2.4/p=0.6)# Eu, etc./ Is: 0.8 (95%CI_0.6-1.2/p=0.3)# Eu, etc./ O West A: 0.7 (95%CI_0.2-2.2/p=0.5)# Eu, etc./ North Af: 0.6 (95%CI_0.2-1.9/p=0.4)# Eu, etc./ Eu, etc.: 0.9 (95%CI_0.6-1.2/p=0.3)#
Smith G. N, 2006 British Columbia, Canada	Retrospective (10-59 years old) Period: from 1902 to 1913. Case identification: admission and discharge register of Provincial Mental Hospital of British Columbia Diagnosis Assignment-Classification: Trained research assistants abstracted life history and clinical notes for each patient who met the inclusion criteria and GNS reviewed these notes in order to make DSM-IV diagnoses. In most cases, diagnoses were made blind to country of birth but clinical comments about language or cultural differences revealed immigrant status in some cases. Ethnic definition: country of birth.	807(189F) cases* Ethnicity: Canadian: 259(74F)→32.1%* European/British:548(115F)→67.9%* (64% from UK) Mean age at admission: Canadian male: 33.9 Canadian female: 37.0 European/British male: 34.3 European/British female: 37.2 Mean age at migration: 26M / 25.9F (data avaible only for 66% of the sample) number of patients -1902-1905: Can: 57 / Eu/Br: 78 -1906-1909: Can: 87 / Eu/Br: 138 -1910-1913: Can 115 / Eu/Br: 332	Standardized Incidence R atio 1902-1905: Can: 1.00 (95% CI_0.76-1.30)/ Eu/Br: 1.20 (95% CI_0.95-1.50)# 1906-1909: Can: 1.30 (95% CI_1.06-1.58)/ Eu/Br:1.30 (95% CI_1.09-1.50) 1910-1913: Can: 0.95 (95% CI_0.79-1.14)# / Eu/Br: 1.94(95% CI_1.73-2.15) The overall effect of **migration** was significant (IRR 1.54, 95%CI_1.33–1.78), and incidence increased over time in the immigrant but not the Canadian-born population. A substantially increased risk in migrants was evident by 1913.The Poisson regression analysis indicated that risk increased 1.04 times per year in immigrants (95% CI_1.02–1.06) and was greater in older age groups (IRR=1.11, 95%CI_1.06–1.19). Women were at lower risk for developing schizophrenia than **men** (IRR 0.44, 95%CI_0.37–0.52).
Leão TS, 2005 Sweden	Prospective cohort study of second generation immigrants aged 16-34 Followed until first hospital admission for mental disorders, death, emigration, or end of study. Period: 1 January 1995-31 December 1998 Case-identification: data of first hospital admission were obtained from a research database at the Karolinska Institute. Diagnosis Assignment-Classification: ICD-9 and ICD-10 which replaced the previous on 1 January 1997	1914703(48.5% F) Sw:1656987 (86.6%*) One parent Sw:176152 (9%*) 2nd Finns: 43080 (2.3%*) 2nd labour: 4786 (0.3%*) 2nd refugee: 33698 (1.8%*)	Second-generation immigrants with one parent born in Sweden and second-generation Finns had a higher risk than the Swedish majority population of being hospitalized for psychotic disorders, affective disorders, neurotic disorders, and personality disorders. Second-generation Finns HR 2.42 (95%CI_2.09-2.80) Second generation with one parent born in Sweden HR 1.51 (95% CI_1.38-1.66) Second-generation refugees HR 1.71 (95%CI_1.39- 2.10).

	1. Psychotic disorders (ICD-9: 295, 297, 298.C, 298.E, 298.W, 298.X and ICD-10: F20_ F29) 2. Affective disorders (ICD-9: 296, 298.A, 298.B, 300.E, 301.B, 311 and ICD-10: F30_ F39) 3. Neurotic disorders (ICD-9: 300.A, 300.B, 300.C, 300.D, 300.F, 300.G, 300.H, 300.W, 300.X, 306, 308, 309 and ICD-10: F40_ F48) 4. Personality disorders (ICD-9: 301.A, 301.C, 301.D, 301.E, 301.F, 301.G, 301.H, 301.J, 301.W, 301.X, 302 and ICD-10: F60_ F69) Ethnic definition: -2nd genation Finns: Swedish-born individuals with both parents born in Finland or one parent born in Finland and one parent born outside Sweden and Finland. -2nd generation labour immigrants: Swedish-born individuals with both parents born in labour immigrant countries or one parent born in labour immigrant countries and one parent born outside Sweden, Finland, and labour immigrant countries. -2nd generation refugees: Swedish-born individuals with both parents born outside Sweden, Finland, and labour immigrant countries (mainly refugee countries). Population at risk: Census	Mean age: - Generation: only second generation	
Hjern A. 2004 Sweden	Cohort study of 1.47 million adults (born 1929–1965) and 1.16 million children and youth (born 1968–1979) in family households from the national census of 1985. The adult study group consisted of the Swedish majority population (=Swedish-born) and first generation immigrants (foreign-born who had settled in Sweden after their twentieth birthday.). The youth study group consisted of Swedish majority population (=child as well as all adults in the household were born in Sweden) and second generation immigrants (= Swedish- and foreign-born children in households where all adults in the household were foreign-born). Period: January 1991 until December 2000 Case identification: data from National Hospital Discharge Register Diagnosis Assignment-Classification: Schizophrenia was defined by a main diagnosis of 295, but excluding 295E, 295F and 295H (ICD-9) (WHO, 1989) in 1991–1996 and F20 (ICD-10) (WHO, 1992) in 1997–2000. 'Other psychoses ' were defined by (a) main diagnosis of 295E, F, H, 296–298 (ICD-9) in 1991–1996 and F21–29, F302, F312, F315, F333 (ICD-10) in 1997–2000 and (b) no hospital discharge that fulfilled the criteria of schizophrenia defined above. Ethnic definition: country of birth for the first generation, country of birth of the female head of the household for the second generation Western: Norway, Denmark, Iceland, germany, Great Britain, USA and Canada, Other western. Eastern Europe: Poland, Hungary, Other Eastern Europe. Southern Europe: Yugoslavia, Greece, Italy, Other southern Europe. Non Europeans: Middle est(Turkey, iran, Iraq, other middle east),	Schizofrenia: Youth study group: Swedish 1 056 225→1339 cases - Second generation immigrants Finland 35 534→114 cases West Eu 9 562→16 cases East&South Eu 22 746→61 cases Non Eu 20 146→1588 cases All 1 144213→ 1588 cases Adult study group: Swedish 1 328 405→1 030 cases -First generation immigrants Finland 56 076→103 cases Western Eu 31 453→27 cases East&South Eu 35 598→ 67cases Non Eu 20 803→ 41cases All 1 472 335→ 1268 cases Other psychosis: Youth study group: Swedish 1 056 225→ 2 710cases - Second generation immigrants Finland 35 534→180cases West Eu 9 562→27cases East&South Eu 22 746→92 cases Non Eu 20 146→87cases	M1:model 1: adjusted for sex and age; M2:model 2: adjusted for sex, age, residency, single adult households, unemployment, white collar socio-economic status and social welfare. RR for Schizophrenia Youth study group: Swedish M1→ 1 / M2→1 - Second generation immigrants Finland **M1→ 2.5** (95%CI_2.1-3.1) / **M2→ 2.0** (95%CI_1.6-2.4) West Eu **M1 → 1.4** (95%CI_0.8-2.2) #/ **M2→1.1** (95%CI_0.7-1.7)# East&South Eu **M1→ 2.2** (95%CI_1.7-2.9) / **M2→1.6** (95%CI_1.2-2.3) Non Eu **M1→ 2.5** (95%CI_1.9-3.3) / **M2→1.3** (95%CI_1.0-1.7) Adult study group: Swedish M1→ 1 / M2→1 - First generation immigrants Finland **M1→ 2.6** (95%CI_2.1-3.2) / **M2→ 1.6** (95%CI_1.3-2.0) West Eu **M1 → 1.4** (95%CI_1.0-2.1) / **M2→1.0** (95%CI_0.7-1.5)# East&South Eu **M1→ 3.1** (95%CI_2.2-4.4) / **M2→1.7** (95%CI_1.2-2.4) Non Eu **M1→ 2.1** (95%CI_1.3-3.4) / **M2→0.4** (95%CI_0.3-0.7)# RR for Other psychosis Youth study group: Swedish M1→ 1 / M2→1 - Second generation immigrants Finland **M1→ 2.0** (95%CI_1.7-2.3) / **M2→ 1.7** (95%CI_1.4-2.0) West Eu **M1 → 1.2** (95%CI_0.8-1.7)# / **M2→0.9** (95%CI_0.6-1.4)# East&South Eu **M1→ 1.7** (95%CI_1.4-2.1) / **M2→1.4** (95%CI_1.1-1.7)

	Asia, latin America, Africa. Population at risk: national census of 1985	All 1 144213→ 3 096 cases Adult study group: Swedish 1 328 405→ 6148 cases -First generation immigrants Finland 56 076→423cases Western Eu 31 453→159 cases East&South Eu 35598→292cases Non Eu 20 803→ 120cases All 1 472 335→ 7142cases	Non Eu **M1→ 1.9** (95%CI_1.5-2.3) / **M2→1.3** (95%CI_1.0-1.6) Adult study group: Swedish M1→ 1 / M2→1 - First generation immigrants Finland **M1→ 1.6** (95%CI_1.4-1.7) / **M2→ 1.3** (95%CI_1.2-1.4) West Eu **M1 → 1.2** (95%CI_1.0-1.4) / **M2→1.0** (95%CI_0.9-1.3)# East&South Eu **M1→ 1.9** (95%CI_1.6-2.3) / **M2→1.5** (95%CI_1.3-1.8) Non Eu **M1→ 1.0** (95%CI_0.8-1.4))#/**M2→0.5** (95%CI_0.4-0.6)# 65% of the second generation immigrant study group was born in Sweden and another 21% had settled in Sweden before school-age. In an analysis that included only the second generation immigrants it was demonstrated that the age and sex-adjusted RR for a psychotic illness was slightly higher in those being born outside Sweden compared with those who were born in Sweden (RR 1.2, 95% CI_1.1–1.3). **All socio-economic household indicators contribute to the reduction of RRs but the greatest reduction is seen for the indicator receiving social welfare.**
Sundquist K, 2004 Sweden	Were investigated the entire Swedish population, in total 4.4 million woman and men aged 25-64 years, until first admission to hospital for treatment of psychosis or depression, death from any cause, emigration from Sweden, or until the end of the study. A total of 35 727 individuals with previous hospital admission for psychosis or depression during 1992-1996 were excluded. Period: from 1 January 1997 to 31 December 1999 Case identification: Swedish Hospital Discharge Register at the National Board of Health and Welfare. Diagnosis Assignment-Classification: psychosis (ICD–9 codes 295, 297, 298C, 298E, 298W, 298X; and ICD–10 codes F20–25, F28, F29) Ethnic definition: Immigrant status was classified into three groups. The first group consisted of people born in countries with mainly labour-related immigration to Sweden (southern European countries and member states of the Organization for Economic Co-operation and Development); the second group consisted of people born in countries often referred to as refugee countries (Eastern European countries, Bosnia, and all other non-European countries); the third group consisted of Swedish born people.	6163* (3133 F) cases Immigrant status (Psychosis and depression): Labour: 307 781 (148564F)* Refugee: 259 402 (131294F)* Swedish:3 870 307 (1 968 443F)* Generation: not specified	Hazard ratio for immigrant woman: Swedish-born: 1 Labour migrant: 1.51 (95%CI_1.35-1.69) Refugee: 1.77 (95%CI_1.57-1.99) Hazard ratio for immigrant men : Swedish-born: 1 Labour migrant: 1.34 (95%CI_1.17-1.52) Refugee: 2.06 (95%CI_1.83-2.32)
Selten J.P. 2003 Netherlands	Retrospective (all institutions for in-patient psychiatric care in the Netherlands) All first episode psychosis cases, aged 15-54. Period: from 1990 to 1996. Case-identification: Dutch Psychiatric Registry. Diagnosis Assignment-Classification: ICD-9; manic-depressive psychosis (MDP), manic type (ICD-9: 296.0) or circular type (296.2: currently manic; 296.3: currently depressed; 296.4: mixed; 296.5: circular type, current condition not specified), schizoaffective disorder (ICD: 295.7). Ethnic definition: country of birth.	Manic-depressive psychosis: Maniac or circular type cases: 6029(3413F) D: 5777→95.8%* S: 94→1.6%* Na: 42→0.7%* T: 66→1.1%* M: 50→0.8%*	MDP, manic or circular type: The risks of a first hospitalization were significantly increased for immigrants from the Na (age- and sex-adjusted RR=1.41; 95%CI_1.10–1.80), not in those from S (age- and sex-adjusted RR=1.13; 95%CI_0.97–1.33). In T and M immigrants, the associations between country of birth and risk of illness interacted with sex as well as with age, the risks being significantly higher for **men and for the younger age** groups. The results for T male aged 15-24 showed a 2.1 RR (95%CI 1.3-3.5), for M male of 1.5 RR (95%CI_0.9-2.3) and decreased risks for older age group. The patterns for female immigrants from these countries (T and M) were also strongly influenced by age. The risk for the age group 15–24 was similar to that for Dutch-

	Population at risk:: The Dutch Central Bureau for Statistics provided yearly figures for populations born in the Netherlands, Surinam, the Netherlands Antilles, Turkey and Morocco, broken down by sex and 5-year age categories.	Depressed type cases: 8720 (6027F) D: 8352→95.8%* S: 101→1.1%* Na: 31→0.4%* T: 130→1.5%* M: 106→1.2%* Mean age: - Generation: second generation is included in Dutch –born group.	born peers, but the risks for the older age groups were significantly decreased. MDP, depressed type: The interactions between the variables country of birth and sex were, again, statistically significant for T (RR 1.83(95CI%_1.46-2.30)) and M (RR 2.17 (95%CI_1.72-2.73)), whereas the interactions with age were not significant in any immigrant group. Risks for female immigrants from all countries were significantly decreased (vs. Dutch-born females)
Selten J. P, 2002 The Netherlands	Were compared the risk of a first admission to a Dutch mental hospital for schizophrenia for Surinamese-born immigrants to the risk for Dutch-born individuals (aged 15-39), using the Surinamese-born population in the Netherlands and the population of Surinam combined as the denominator for the immigrants. Period: 1983-1992. Case identification: Dutch psychiatry registry Diagnosis Assignment-Classification: ICD-9 Ethnic definition: country of birth.	Same sample of Selten 1997	Relative risk of first admission for Surinamese born population of the Netherlands: Men 4.45 (95%CI_4.06-4.88) Woman 2.80 (95%CI_2.44-3.23) After enlargement of the denominator by adding the resident population of Surinam, the risk of first hospital admission for schizophrenia among immigrants from Suriname remained significantly higher than that for Dutch born peers. The selection hypothesis could be rejected Men 1.67 (95%CI_1.52-1.83) Woman 1.12 (95%CI_0.97-1.29)#
Mortensen P. B, 1997 Denmark	All individuals who were recorded in the Danish Psychiatric Case Register as having been admitted for the first time in their lives for a psychiatric disorder. it was decided to supplement this analysis with a case-control study where the cases consisted of all individuals admitted for the first time with a diagnosis of schizophrenia and the controls were seven individuals with non-psychotic diagnoses per case, randomly selected and matched for ad-mission year. Period: 1980-1992 Case identification: Danish Psychiatric Case Register Diagnosis Assignment-Classification: ICD-8: schizophrenia, non affective functional psychosis, maniac-depressive psychosis and affective psychosis. Ethnic definition: country of birth. Population at risk: relative risk were calculated separately for males and females and were adjusted for age using indirect standardization.	Immigrant cases: -Schizophrenia:143 (41F) -Non affective functional psychosis: 725 (306F) -Maniac-depressive psychosis: 262(159F) -Affective psychosis: 593 (333F) Generation: only first	Relative risk among immigrants to Denmark, based on population rates: -Schizophrenia: Males 1.71 (95%CI_1.40-2.08) Females 1.68 (95%CI_ 1.20-2.28) Total 1.70 (95%CI_1.44-2.01) -Non affective functional psychosis: Males 2.10 (95%CI_1.91-2.32) Females 1.70 (95%CI_1.51-1.90) Total 1.91 (95%CI_1.77-2.06) -Maniac-depressive psychosis: Males 0.80 (95%CI_0.65-0.96) Females 0.74 (95%CI_0.63-0.86) Total 0.76 (95%CI_0.67-0.85) -Affective psychosis: Males 1.16 (95%CI_1.02-1.31) Females0.95 (95%CI_0.85-1.06)# Total 1.03 (95%CI_0.95-1.12))# Relative risk for schizophrenia versus non psychotic disorder among immigrants to Denmark (case-control study) Total born outside Denmark: 1.34 (95%CI_1.09-1.64) EU and Scandinavia 1.48 (95%CI_1.11-1.98) Yugoslavia 0.92 (95%CI_0.21-4.03)# Turkey 0.89 (95%CI_0.35-2.25)#

			Pakistan 0.82 (95%CI_0.19-3.54)# Other 1.32 (95%CI_0.98-1.78)#
Selten J P, 1997 The Netherlands	Were calculated the risk of first admission for schizophrenia for people aged 15-39 in Netherlands. The registry selected data on all Dutch-, Surinamese- and Netherlands Antillean born patients Period:1983-1992. Case identification: data from the Dutch psychiatric registry Diagnosis Assignment-Classification: ICD-9: data set 1:"broad schizophrenia" data set 1: "Restricted schizophrenia" which include subtypes of catatonic, paranoid and hebephrenic schizophrenia. Ethnic definition: country of birth. Population at risk: central Bureau for Statistics provided yearly figures for: S and Na born population in The Netherlands, broken down by sex and 5 years categories; and the total Dutch population (same sex and age categories).	Ethnicity: Data set 1 "broad schizophrenia" D: 10 726* (4039F) S: 697* (203F) Na: 236*(68F) Data set 1 "restricted schizophrenia" D: 4933* (1567F) S: 390* (100F) Na: 125* (29F) Generation not specified	The sex- and age-adjusted relative risk of a First admission for `broad schizophrenia' (ICD-9 criteria; data-set 1) was 3.8 (95% Confidence Interval: 3.5 to 4.1) for Surinamese-born immigrants and 3.9 (3.5 to 4.5) for the Antillean born immigrants. The sex and age adjusted relative risk of a first admission for "broad schizophrenia" was: S: M 4.5(95%CI_4.1-4.9) F 2.8(95%CI_2.4-3.2) Na:M 4.5(95%CI_3.9-5.3) F 3.0(95%CI_2.3-3.8) While for "restricted schizophrenia" was S: M 5.2(95%CI_4.6-5.8) F 3.6(95%CI_2.9-4.4) Na:M 5.1(95%CI_4.2-6.3) F 3.3(95%CI_2.3-4.7) The age-adjusted relative risks were as much increased in **Surinamese immigrants** as in Dutch Antilleans. These results remained essentially unchanged when we varied the type of schizophrenia (`broad' or ` restricted ') and the required number of hospitalizations (at least one or two, in data-sets 1 and 2 respectively). Interestingly, the age-adjusted relative risks were significantly higher for **male** than for female immigrants.
Bland 1981 Edmonton, Canada	This study is based on a group of patients with schizophrenia who had their first lifetime admission to Alberta Hospital Edmonton in 1963. This approximates an incidence by first admission group of patients from a population of 663.000. Period: 1963 Diagnosis Assignment-Classification: who fulfilled two or three of the diagnostic criteria: 1-Feighner et al for schizophrenia or probable schizophrenia; 2-Scheneider's first rank symptoms 3-New Haven Schizophrenia Index Ethnic definition: place of birth. Population at risk: 1961 Census of Canada report.	43 cases(21F) Mean age: 34.5 M 30.6F Ethnicity: 10migrants: 8 European Generation: not specified	The immigrants from Eastern Europe accounts for 25% of the immigrant population in Alberta, but accounted for 8 (80%) of the immigrants schizophrenics (p<0.005). The expectancy (summation) for schizophrenia in Eastern European males immigrating to Alberta between 1956 and 1961 was calculated at 6.49%, thirteen times that found for population as a whole. This difference was tested and despite small numbers, was found to be significant (p<0.025), so that this groups seems to be at high risk. Census data on "mother tongue" (2/3 of the Alberta population claim English as their mother tongue) were compared to the mother tongue of the patients. Slightly more than the expected number of patients were English speaking, less than expected belonged to other major language groups and significantly more than expected claimed an unspecified minority language as their mother tongue (p<0.005).
GP setting : 2			
Schofield P, 2011 Lambeth, South East London. UK	Retrospective Were analyzed general practitioner records, over a 10 years period, from a sample of practices in Lambeth. All cases aged 16-74. Period: from January 1996 to November 2006. Case identification: Diagnosis was determined from Read codes entered in the GP records together with the earliest date of diagnosis. Diagnosis Assignment-Classification: Read code: patients with a first diagnosis of a psychotic illness, defined as any non-organic psychosis and excluding drug-induced disorders. Ethnic definition: "black or black British" 2001 UK census ethnic	Sample: 60971(54%F) Mean age of total sample: 35 Ethnicity: B: 23693(25%) W: 37278(61%) Ethnic density quintile: 5th quintile (most dense): 43% 4th quintile: 31%	Adjusting for age and gender gave an overall psychosis incidence rate ratio (IRR) of 2.14 (95%CI_1.61–2.85) when comparing black and white participants. Were found that black people in areas with t 25 % B or a higher ethnic density showed no significant difference in psychosis rates compared with the white population. Conversely, black people in lower than average ethnic density areas were nearly three times more likely (odds ratio (OR) 2.88, 95% CI_1.89–4.39) to develop a psychotic illness compared with their white counterparts in the same area. While the effect of area deprivation is not significant in the unadjusted model, it is revealed as a contributory factor after adjusting for the effect of neighborhood ethnic density. This suggests that the negative effects of social deprivation are therefore

	category. Population at risk: census data and data collected from the Health and Social Care Information Centre. Ethnic density, defined as the proportion of black people in a given neighbourhood, was determined by matching patient postcodes to LSOA and the ethnic profile of each LSOA was determined using 2001 census data.	3th quintile 24% 2th quintile: 19% 1th quintile (least dense): 11% Average neighborhood composition: 25% B FEP:196(44%F) Ethnicity: B: 109 (55.6%*) W: 87 (44.4%*) Mean age (FEP): 37M; 42F Generation: not specified	smaller than, and work in the opposite direction to, the **ethnic density** effect and are therefore cancelled out in the unadjusted model. -High density (25–62% black) unadjusted: IRR 1.41 (95%CI_0.95–2.09); adjusted (age, gender and area deprivation score): IRR 1.48 (95%CI_0.98–2.23) -Low density (0–24% black) unadjusted: IRR 2.75 (95%CI_1.82–4.15); adjusted (age, gender and area deprivation score): IRR 2.88 (95%CI_1.89–4.39);
Selten 2001 The Hague, The Netherlands	Prospective All subjects aged 15-54 years who made first contact with a physician for a suspected psychotic disorder. Period: 1 April 1997- 1 April 1999. Case Identification: all subjects 15-54 years who made first contact with physician (GPs and psychiatrists) for a (suspected) psychotic disorders [**subject whose residence was shorter than 6 month or who stayed illegally were excluded].** Research interview: CASH (Comprehensive Assessment of Symptom and History, Andreasen et al., 1992), IRAOS (Retrospective Assessment of the Onset of Schziphrenia, Hafner et al., 1992) Diagnosis Assignment: During a diagnostic meeting 2 psychiatrists who remained blind to ethnicity made a consensus DSM-IV diagnosis: schizophrenia, schizophreniform disorder, schizoaffective disorder, major depressive or bipolar disorder with psychotic features, delusional disorder, brief psychotic disorder, psychotic disorder not otherwise specified. Ethnic definition: census information; citizens' country of birth and that of their parents. Population at risk: the population figures in each neighbourhood for 1 January 1998, by 5-year age group, gender and country of birth of citizen and parents, were made avaible by the city of The Hague. The 40 neighborhoods of the Hague are divided into five socio-economics levels, based on disposable income, quality of housing and rates of long term unemployment. Relative risk were adjusted for age and gender and socio-economic status.	197 patients, 152 diagnostic interview (no differences between refusers and patient who consented) 12 patients excluded because substance induced psychosis and 4 patients because the presence if psychosis was dubious Final sample :181 patients (126 man, 55 women) Men age : men 28.3 (±9.2); women 32.0 (±9.5) Ethnicity : (First and second generation combinated) Natives: 65(21F) S: 31*(14F) Na: 6*(1F) T: 10*(1F) M: 26*(2F) O: 25*(16F)	Rates for all psychotic disorders 3.5 (95%CI_3.0-4-0) per 10 000. Rates for schizophrenic disorders (schizophrenia, schizophreniform, schizoaffective disorder) 2.1 (95%CI_1.7-2.5) per 10 000.. RR of any psychotic disorders significantly increased for immigrants from Surinam, The Netheralnd Antilles, Morocco and other non-Western countries, but not from Turkey and Western or Westernised countries (Eu, USA, Canada, Australia, New Zeland, Japan, Israel) I generation / All psychotic disorder / Schizophrenic disorder Natives: 1 / 1 Surinamese: 2 (95%CI_1.2-3.3) / 3.2 (95%CI_1.8-5.7) Netherlands Antilleans: 3.2 (95%CI_1.4-7.5) / 2.9 (95%CI_0.9-9.5)# Turks: 1.5 (95%CI_0.8-2.9)# / 0.8 (95%CI_0.2-2.6)# Moroccan: 4.3 (95%CI_2.7-7.1) / 4.5 (95%CI_2.4-8.5) Other, Western or Westernized: 1.0 (95%CI_0.4-2.4)# / 1.1 (95%CI_0.3-3.6)# Other, non-Western: 2.4 (95%CI_1.5-3.9) / 2.4 (95%CI_1.3-4.7) The RR was increased for Moroccan and Surinamese II generation II generation / All psychotic disorder / Schizophrenic disorder Natives: 1 / 1 Surinamese: 4.6 (95%CI_2.2-9.3) / 5.5 (95%CI_2.5-11.9) Moroccan: 9.3 (95%CI_3.7-23.4) / 8.0 (95%CI_2.6-24.5) Other: 1.4 (95%CI_0.6-3.2)# / 1.7 (95%CI_0.7-4.1)# The higher RR was found for Moroccan (I and II generations) with an high proportion of men among Moroccan FEP The excess of psychosis disorders in the immigrant groups was not explained by the socioeconomic status of their neighborhood. Relative Risk adjusted for age and gender, then for age, gender and socio-economic status of neighbourhood: I&II gener. / All psychotic disorder / / Schizophrenic disorder / / Natives: 1 / 1 / 1 / 1 S: 2(1.4-3.7) / 2.0(1.2-3.3) / 3.5(2.0-6.2) / 3.1(1.7-5.7) Na: 4.1(2.0-8.7) / 3.7(1.8-7.9) / 1.8(0.4-7.4)# / 1.6(0.4-6.9)# T: 0.9(0.4-2.1)# / 0.7(0.3-1.8)# / 0.2(0.0-1.8)# / 0.2(0.0-1.6)# M: 4.9(3.0-7.9) / 4.0(2.9-10.2) / 5.5(2.9-10.2) / 4.7(2.4-9.2) Other: 1.6(1.0-2.4) / 1.5(1.1-3.6) / 2.0(1.1-3.6) / 1.9(1.1-3.4)

			Most immigrants had been brought to The Netherland by their parents. The majority of key informants regarded the patients most prominent symptoms as abnormal within his or her culture

***:** Values calculated and adapted by the authors of the review;
#: values not statistically significant;

BOLOGNA MIGRATION HISTORY AND SOCIAL INTEGRATION

(FOR FIRST GENERATION MIGRANTS) CORE Interview

STUDIE: EU GEI **Subject number:** |__|EU|__|__|-|__|__|__|__|	**Date of Birth** |__|__|-|__|__|-|1|9|__|__|
Time interval: **Interviewer:**	**Period – Replicat** |0|__|-|0|__| **Date** |__|__|-|__|__|-|2|0|__|__|

A - Before migration

1. **Who did you live with in your country of origin, immediately prior to migrating?**

O1 Alone | O2 Alone, with children | O3 Partner/Spouse | O4 Partner/Spouse, with children

O5 Parents | O6 Other family | O7 Friends | O8 Other (specify): .....

2. **Were you ever employed in your country of origin?** O0 No O1 Yes

3. **What was your employment in your country of origin, immediately prior to migrating?**

O1 Unemployed	O2 House person
O3 Physical-illness disability	O4 Retired
O5 Carer	O6 Student
O7 Employed	O8 Part-time employee
O9 Full-time employee	O10 Self-employed

4. **Social class**

(provide descriptions only) **Main (In your country of origin)**

a. **Job Title** _____

b. **What did you mainly do?** _____

c. **What did organization make?** _____

d. **Social class subject**

O1 Higher grade Professional	O2 Lower grade Professional
O3 Intermediate occupations	O4 Small Employer and self employed occupations
O5 Self employed occupations	O6 Lower supervisory and lower technician occupations
O7 Lower services, sales and clerical occupations	O8 Lower technical occupations
O9 Routine Occupations	O10 Never worked and long-term unemployed

B- Migration Process

1. **Date of Migration** |__|__|-|__|__|-|__|__|__|__|

2. **What's the reason why you left your country?**

O1. Working O2 Studying

O3 Wedding O4 Family Reunion

O5 Asylum seeking O6 Other political reason

O7 Tourism O8 Health

O9 Other

2.1 Please specify other: .....

3. **Have you ever been detained because you did not have a residence permit or leave to remain in this country** O0 No O1 Yes

4. **If yes, how long?** |__|__| Months

5. **Do you consider this country the last step of migration?** O0 No O1 Yes

5.1 If no, please specify why (if several options are satisfied, please indicate the main):

O1 Economic reasons (e.g. low incomes, high cost of living, can't find a job …)

O2 Family reasons (e.g. want to join a member of my family living somewhere else, want to walk off from a family member living here …)

O3 Socio-environmental factors (e.g. don't fit in the new environment, unsuccessful integration, low quality of life, discrimination …)

O4 Expulsion/Residence permit expired

O5 In trouble/need to escape (e.g. from someone, from law …)

O6 Never meant to stay in this country / always considered as a "passage country"

O7 Other

5.2 Please specify other: .....

6. **Do you plan to permanently return to your country of origin one day?** O0 No O1 Yes

6.1 If no, please specify why (if several options are satisfied, please indicate the most important):

O1 There is no family/home anymore O2 No prospects in country of origin (i.e., no work)

O3 Risks in country of origin (e.g., war, persecution) O4 Cost is too high

O5 disowned by family/ashamed of going back O6 doesn't want to see certain people

O7 wants to see other places O8 doesn't want to go back to old lifestyle

O10 His/her life is here O11 Other

6.2 Please specify other:.....

C- Post Migration

1. **Do you have a residence permit or permanent leave to remain?** O0 No O1 Yes

2. **What is your migrant status?**

O1 Undocumented O2 Asylum seekers

O3 Refugee O4 Temporary resident

O5 European Citizen O6 Citizen of this country

O7 Stateless O8 Other

2.1 Please specify other:.....

3. **Do you have family or friends in this country?** O0 No O1 Yes

3.1 If yes, who:

O1 Alone, with children O2Partner/Spouse O3 Partner/Spouse, with children

O4Parents O5 Other family O6Friends

3.2 Please specify other family: ……...

4. **Do you have family in your country of origin?** O0 No O1 Yes

4.1 If yes, who:

O1 Children O2 Partner/Spouse O3 Partner/Spouse, with children

O4Parents O5 Other family

4.2 Please specify other family: ……...

5. **How often do you travel back to your country of origin?**

O1 Often (2 or more times per year)

O2 Yearly (1 time per year)

O3 Infrequent (Less than once per year)

O4 Never

6. **How has your work position changed since you left your country of origin**?

O1 Better

O2 Worse

O3 Unchanged

7. **How has your economic position changed since you left your/your parent's country of origin?**

O1 Better

O2 Worse

O3 Unchanged

8. **Please indicate, in relation to each of the following areas, the extent to which your expectations have been achieved:**

	Perfectly achieved	Partially achieved	Poorly achieved	Not achieved at all
Work	O1	O2	O3	O4
Income	O1	O2	O3	O4
Family	O1	O2	O3	O4
Health	O1	O2	O3	O4
Friends and social network	O1	O2	O3	O4
Other	O1	O2	O3	O4

Any problems conducting the interview? O0 No O1 Yes

If yes, specify:

……

BOLOGNA MIGRATION HISTORY AND SOCIAL INTEGRATION

(FOR FIRST GENERATION MIGRANTS) IN DEPT INTERVIEW

STUDIE: EU GEI **Subject number:** |__| EU |__|__|- |__|__|__|__|	**Date of Birth** |__|__|-|__|__|-|1|9|__|__|
Time interval: **Interviewer:** ……	**Period – Replicat** |0|__|-|0|__| **Date** |__|__|-|__|__|-|2|0|__|__|

A - Before migration

1. **What type of accommodation did you live in immediately before you migrated?**

O1 Privately owned (self) O2 Privately owned (family) O3 Rented (private)

O4 Rented (government) O5 Other

1.1. Please specify other: _____

2. **What was your relationship status immediately before you migrated?**

O1Single O2 Married/Living with someone O3 In a steady relationship

O4 Divorced, Separated O5 Widowed

3. **Satisfaction with life**

	Very high	**high**	**intermediate**	**low**	**Very low**
a) Health	O1	O2	O3	O4	O5
b) Work	O1	O2	O3	O4	O5
c) Family/relationships	O1	O2	O3	O4	O5
d) Social relations	O1	O2	O3	O4	O5

4. **Preparation for migration (adapted from Ryan et al., 2006)**

4.1 For how long did you prepare your migration?

O1 Some days O2 Some weeks

O3 Some months O4 Some years

4.2 Did you discuss your migration with family members? O0 No O1 Yes

4.3 Did you obtain family agreement with your decision? O0 No O1 Yes

4.4 Did you pre-arrange employment? O0 No O1 Yes

4.5 Did you considered your length of stay? O0 No O1 Yes

4.6 Did you have a network of friends or family available upon arrival? O0 No O1 Yes

4.7 Did you pre-arrange accommodation? O0 No O1 Yes

4.8 Did you make plans for a longer stay? O0 No O1 Yes

B- Migration Process

1. **Did you/your parents get into any debt to pay for migrating?** O0 No O1 Yes

2. **If yes, who provided you/your parents with the money to migrate?** O1 Family members O2 Friends O3 Other

2.1. Please specify other: _____

3. **Have you/your parents now paid this debt?** O0 No O1 Yes

4. **Do you/your parents have any problems related to the payment of this debt?** O0 No O1 Yes

4.1 If yes, please specify: O1 Economic O2 Religious/Spiritual O3 Other

4.2 Please specify other:_____

5. Why did you decide to come to this country? _____

6. With whom did you travel during migration?

O1 Alone O2 Alone, with children O3Partner/Spouse O4 Partner/Spouse, with children

O5 Parents O6 Other family O7 Friends O8 Other

6.1 Please specify other: _____

7. Did you spend more time than you expected travelling to this country? O0 No O1 Yes

7.1 If yes, please specify why : _____

C- Post Migration

1. Social support in the post-migration country

		Very high	high	intermediate	low	Very low
a)	From compatriots in this country	O1	O2	O3	O4	O5
b)	From compatriots in country of origin	O1	O2	O3	O4	O5
c)	From citizens of this country	O1	O2	O3	O4	O5
d)	From social workers and/or voluntaries in this country	O1	O2	O3	O4	O5

Any problems conducting the interview? O0 No O1 Yes

If yes, specify: _____